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(54) **BICYCLIC COMPOUNDS USEFUL AS GPR120 MODULATORS**

BICYCLISCHE VERBINDUNGEN VERWENDBAR ALS GPR120-MODULATOREN

COMPOSÉS BICYCLIQUES UTILES EN TANT QUE MODULATEURS DU GPR120

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(56) References cited:

| | |
|---------------------|---------------------|
| EP-A1- 0 548 934 | EP-A1- 2 172 198 |
| EP-A2- 0 145 078 | WO-A1-96/26195 |
| WO-A1-03/033480 | WO-A1-2006/020879 |
| WO-A1-2010/104195 | WO-A1-2014/086663 |
| WO-A1-2014/096941 | WO-A1-2015/150565 |
| WO-A1-2016/033436 | WO-A2-2005/037779 |
| WO-A2-2007/109211 | WO-A2-2010/048207 |
| DE-A1- 2 253 251 | US-A- 5 334 600 |
| US-A1- 2009 275 578 | US-A1- 2010 035 944 |
| US-A1- 2011 245 247 | US-A1- 2011 312 976 |
| US-A1- 2014 275 182 | US-A1- 2015 291 527 |

- WITTY DAVID R ET AL: "Discovery of potent and stable conformationally constrained analogues of the MCH R1 antagonist SB-568849", BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 16, no. 18, 12 July 2006 (2006-07-12), pages 4872-4878, XP028596898, ISSN: 0960-894X, DOI: 10.1016/J.BMCL.2006.06.061

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- FELLS J I ET AL: "Structure-based drug design identifies novel LPA"3 antagonists", BIOORGANIC & MEDICINAL CHEMISTRY : A TETRAHEDRON PUBLICATION FOR THE RAPID DISSEMINATION OF FULL ORIGINAL RESEARCH PAPERS AND CRITICAL REVIEWS ON BIOMOLECULAR CHEMISTRY, MEDICINAL CHEMISTRY AND RELATED DISCIPLINES, ELSEVIER, NL, vol. 17, no. 21, 1 November 2009 (2009-11-01), pages 7457-7464, XP026691221, ISSN: 0968-0896, DOI: 10.1016/J.BMC.2009.09.022 [retrieved on 2009-09-18]
- FELLS J I ET AL: "2D binary QSAR modeling of LPA"3 receptor antagonism", JOURNAL OF MOLECULAR GRAPHICS AND MODELLING, ELSEVIER SCIENCE, NEW YORK, NY, US, vol. 28, no. 8, 1 June 2010 (2010-06-01), pages 828-833, XP027045036, ISSN: 1093-3263 [retrieved on 2010-03-07]
- JAYARAMAN SELVAKUMAR ET AL: "Synthesis of Condensed Tetrahydroisoquinoline Class of Alkaloids by Employing TfOH-Mediated Imide Carbonyl Activation : Synthesis of Condensed Tetrahydroisoquinoline Class of Alkaloids", EUROPEAN JOURNAL OF ORGANIC CHEMISTRY, vol. 2015, no. 10, 1 April 2015 (2015-04-01), pages 2175-2188, XP055674470, DE ISSN: 1434-193X, DOI: 10.1002/ejoc.201403617
- GOLBRAIKH A ET AL: "Validation of protein-based alignment in 3D quantitative structure-activity relationships with CoMFA models", EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY, ELSEVIER, AMSTERDAM, NL, vol. 35, no. 1, 1 January 2000 (2000-01-01), pages 123-136, XP004350212, ISSN: 0223-5234, DOI: 10.1016/S0223-5234(00)00108-2
- CHOI YOUNG LOK ET AL: "Synthesis of aristolactam analogues and evaluation of their antitumor activity", BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 19, no. 11, 10 April 2009 (2009-04-10), pages 3036-3040, XP029439845, ISSN: 0960-894X, DOI: 10.1016/J.BMCL.2009.04.020
- MAGALI LORION ET AL: "Complementary Synthetic Approaches to Constitutionally Diverse N-Aminoalkylated Isoindolinones: Application to the Synthesis of Falipamil and 5-HT1A Receptor Ligand Analogues", SYNTHESIS, vol. 2009, no. 11, 14 April 2009 (2009-04-14), pages 1897-1903, XP055674564, STUTTGART, DE. ISSN: 0039-7881, DOI: 10.1055/s-0028-1088048
- FUCCELLA L M ET AL: "Fate of the analgesic and anti-inflammatory drug K 4277 after oral administration to man", EUROPEAN JOURNAL OF CLINICAL PHARMACOLOGY, SPRINGER VERLAG, DE, vol. 6, no. 4, 1 December 1973 (1973-12-01), pages 256-260, XP009519291, ISSN: 0031-6970, DOI: 10.1007/BF00644742

Description**CROSS-REFERENCED TO RELATED PATENT APPLICATION**

5 [0001] This application claims priority from Provisional U.S. Application Serial No. 62/393,619, filed September 12, 2016.

FIELD OF THE INVENTION

10 [0002] The present invention provides compositions and methods for modulating the GPR120 receptor, and generally relates to the fields of medicinal chemistry, medicine, pharmacology, molecular biology, and biology. Compounds modulating the GPR120 receptor are useful for treating various metabolic and inflammatory diseases, including but not limited to, type 2 diabetes, obesity, hepatic steatosis, and Alzheimer's, and one or more symptoms of each thereof.

15 BACKGROUND OF THE INVENTION

[0003] Type 2 diabetes (T2D) is a chronic disease resulting from the body's inefficient use of the insulin it produces. The states of hyperglycemia and insulin resistance observed in T2D typically result from excess weight and lack of physical exercise. Because obesity and sedentary lifestyles are increasing worldwide, the incidence of T2D is also rapidly increasing. The World Health Organization (WHO) estimates that more than 300 million people worldwide have T2D, and that more than 1 million deaths per year can be directly attributed to T2D. WHO furthermore projects that diabetes-associated deaths will increase by 50% over the next decade. Current therapeutic strategies for T2D include treatment with agents that target the secretion or utilization of insulin. However, these strategies do not work or do not work well for all patients, and new strategies and agents are needed for treatment of the multiple aspects of T2D pathology.

20 [0004] GPR120, also known as free fatty acid receptor 4 (FFA4), is a 7-transmembrane-spanning G-protein coupled receptor that is activated by long-chain free fatty acids including the ω -3 fatty acids. GPR120 is expressed in a wide range of tissues and mediates multiple effects associated with energy balance and inflammation. In enteroendocrine cells, activation of GPR120 leads to secretion of the incretins glucagon-like peptide-1 (GLP-1) and gastric inhibitory peptide (GIP), which in turn stimulate release of insulin from pancreatic beta cells. Activation of GPR120 in adipocytes stimulates glucose uptake and adipogenesis while inhibiting lipolysis. Activation of GPR120 in macrophages exerts anti-inflammatory effects, inhibiting the release of cytokines including TNF- α and IL-6. In enteroendocrine cells and adipocytes, GPR120 signaling proceeds through Gq/11, but in macrophages GPR120 signaling proceeds through the β -arrestin pathway. Dysfunction in GPR120 has been associated with diabetes and obesity in both mice and humans. Accordingly, GPR120 agonists have been tested for the treatment of T2D and other metabolic diseases.(1-4)

25 [0005] Hepatic steatosis is a state of inflammation and cell injury associated with the accumulation of fat in the liver. In cases not related to alcohol intake, the disease is known as non-alcoholic steatohepatitis (NASH). NASH is increasingly common, can lead to liver cirrhosis or liver failure, and is often observed in people with obesity, glucose intolerance, or dyslipidemia. Recent studies utilizing wild type and GPR120 deficient mice confirm a positive role for GPR120 in controlling lipid metabolism, triglyceride and diacylglycerol levels, and inflammatory markers. Consistent with these results, a study of children with nonalcoholic fatty liver disease who were treated with the GPR120 agonist docosahexaenoic (DHA) acid resulted in reduced liver damage and inflammatory macrophages, and increased GPR120 hepatocyte expression.(5a).

30 [0006] Alzheimer's disease (AD) is the most common cause of dementia in the elderly, with an estimated 47M cases worldwide at present and an expectation for more than 130M cases by 2050. Recently it has been demonstrated that activation of GPR120 exerts anti-inflammatory effects in immortalized hypothalamic neurons,(6a) and that GPR120 and another long chain free fatty acid receptor, GPR40 (FFA1), control energy homeostasis and inflammation in the mouse hypothalamus (7a). NLRP3 inflammasome activity has been shown to contribute to pathology in APP/PS1 mice (8a). Omega-3 fatty acids block activation of NLRP3 inflammasomes in macrophages, thereby inhibiting downstream activation of caspase-1 and maturation and release of interleukin-1beta (IL-1beta) (9a). Expression of NLRP1 inflammasomes is also upregulated in the brains of APP/PS1 mice, and A β induces NLRP1- and caspase-1 dependent pyroptosis in cultured cortical neurons from these animals (10a). Levels of inflammasome-activated caspase-1 are strongly enhanced in the brains of humans with mild cognitive impairment and AD, and activation of NLRP1 in cultured human neurons induces axonal degeneration (11a). Accordingly, GPR120 agonists hold promise as disease-modifying therapeutics for AD, Parkinson's disease, frontotemporal dementia (FTD), amyotrophic lateral sclerosis (ALS), multi-system atrophy (MSA) and other disorders associated with neuroinflammation.

35 [0007] The present invention provides novel compounds, compositions of matter, particularly pharmaceutical compositions, methods for the synthesis or preparation of the compounds and compositions, and methods for using them to modulate GPR120 and treat T2D, hepatic steatosis, Alzheimer's, and other disease associated with metabolic dysfunction and inflammation.

[0008] The description may encompass subject-matter extending beyond the scope of the claims. However the scope of the invention and of protection is solely defined by the appended claims and shall not extend beyond their scope. In particular, the scope of protection shall not include any method of therapeutic treatment of the human or animal body, even if such subject-matter is disclosed or implied herein.

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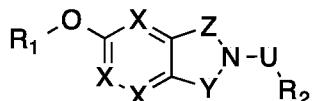
SUMMARY OF THE INVENTION

[0009] The present invention provides, in certain aspects, compounds, compositions of matter (particularly pharmaceutical compositions), methods for the synthesis or preparation of the compounds and compositions, and methods for using them to modulate GPR120.

[0010] Provided herein are compounds, compositions including them, and methods of modulating the GPR120 receptor and treating diseases by administering such compounds and compositions.

[0011] The first aspect of the present invention provides compounds of **Formula I** that in various embodiments comprise a bicyclic core element containing from 9-10 ring atoms, 1-4 ring nitrogen atoms, and up to 3 ring substituents:

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Formula I

as well as tautomers, isotopomers and stereoisomers thereof, and prodrugs of any of the foregoing, and pharmaceutically acceptable salts and solvates of all of the foregoing, wherein each X independently is CH, CR₃, or N; Y is SO₂; Z is -CH₂-, -CH(CH₃)-, -C(CH₃)₂-, -C(CH₂CH₃)-, -(CO)CH₂-, or -CHCH-; U is CH₂, -CH(CH₃)-, -C(CH₃)₂-, or -CH₂CH₂-, R₁ is an optionally substituted alkyl group, an optionally substituted 3-7 membered cycloalkyl or heterocyclyl group, an optionally substituted 5- or 6-membered aryl or heteroaryl group, or an optionally substituted 5,6- or 6,6- bicyclic aryl or heteroaryl group; R₂ is an optionally substituted 3-7 membered cycloalkyl or heterocyclyl group, an optionally substituted 6-membered aryl group, an optionally substituted 5- or 6-membered heteroaryl group, an optionally substituted 5,6- or 6,6- bicyclic heteroaryl group, or an optionally substituted bicyclic aryl group; R₃ is a halogen, or an optionally substituted alkyl or alkoxy group.

[0012] The compounds of Formula I are contemplated to be GPR120 agonists that stimulate release of GLP-1, GIP and/or glucagon, inhibit release of ghrelin, stimulate glucose uptake and/or exert anti-inflammatory effects, and thereby exert therapeutic effects in T2D. In another aspect, provided herein is a method for agonizing GPR120, comprising contacting the GPR120 with a compound or the composition provided or disclosed herein.

[0013] In another aspect, provided herein is a method for modulating metabolism in a mammal, comprising contacting GPR120 in the mammal with an amount of the compound provided herein that is effective to modulate metabolism in the mammal. In another aspect, provided herein is a method for modulating metabolism in a mammal, comprising administering to the mammal an amount of the composition provided herein that is effective to modulate metabolism in the mammal.

[0014] In another aspect, provided herein is a method for reducing inflammation in a mammal, comprising contacting GPR120 in the mammal with an amount of the compound provided herein that is effective to reduce the inflammation. In another aspect, provided herein is a method for reducing inflammation in a mammal, comprising administering to the mammal an amount of the composition provided herein that is effective to reduce the inflammation.

[0015] In another aspect, provided herein is a method for reducing neuroinflammation in a mammal, comprising contacting GPR120 in the mammal with an amount of the compound provided herein that is effective to reduce the neuroinflammation. As used herein, neuroinflammation refers to inflammation of the nervous tissue. In another aspect, provided herein is a method for reducing neuroinflammation in a mammal, comprising administering to the mammal an amount of the composition provided herein that is effective to reduce neuroinflammation.

[0016] In another aspect, provided herein is a method for treating diabetes, pre-diabetes or metabolic syndrome, or one or more symptoms of each thereof in a mammal, comprising contacting GPR120 in the mammal with a therapeutically effective amount of the compound provided herein. In another aspect, provided herein is a method for treating diabetes, pre-diabetes or metabolic syndrome, or one or more symptoms of each thereof in a mammal, comprising administering to the mammal a therapeutically effective amount of the composition provided herein.

[0017] In another aspect, provided herein is a method for treating steatohepatitis in a mammal, comprising contacting GPR120 in the mammal with a therapeutically effective amount of the compound provided herein. In another aspect, provided herein is a method for treating steatohepatitis in a mammal, comprising administering to the mammal a therapeutically effective amount of the composition provided herein.

[0018] In another aspect, provided herein is a method for treating non-alcoholic steatohepatitis in a mammal, comprising

contacting GPR120 in the mammal with a therapeutically effective amount of the compound provided herein. In another aspect, provided herein is a method for treating non-alcoholic steatohepatitis in a mammal, comprising administering to the mammal a therapeutically effective amount of the composition provided herein.

[0019] In another aspect, provided herein is a method for treating a disorder associated with, leading to, or resulting from neuroinflammation in a mammal, comprising contacting GPR120 in the mammal with a therapeutically effective amount of the compound provided herein. In another aspect, provided herein is a method for treating a disorder associated with leading to, or resulting from neuroinflammation in a mammal, comprising administering to the mammal a therapeutically effective amount of the composition provided herein.

[0020] In another aspect, provided herein is a method for treating Alzheimer's disease, Parkinson's disease, fronto-temporal dementia, amyotrophic lateral sclerosis or multi-system atrophy, or one or more symptoms of each thereof, comprising contacting GPR120 in the patient with a therapeutically effective amount of the compound provided herein.

[0021] In another aspect, provided herein is a method for treating Alzheimer's disease, Parkinson's disease, fronto-temporal dementia, amyotrophic lateral sclerosis or multi-system atrophy, or one or more symptoms of each thereof, comprising administering to the patient a therapeutically effective amount of the composition provided herein.

DETAILED DESCRIPTION OF THE INVENTION

[0022] To aid the reader in understanding the invention, how it is made and used, and the benefits thereof, the following usages and definitions are provided.

[0023] All numerical designations, e.g., pH, temperature, time, concentration, and molecular weight, including ranges, are approximations which may be varied (+) or (-) by increments of, e.g., 0.1 or 1. Thus, all numerical designations may be interpreted by the reader as preceded by the term "about". Similarly, the reagents described herein are merely exemplary; generally, the artisan of ordinary skill will appreciate that equivalents of such are known in the art. As used in the specification and claims, the singular forms "a", "an" and "the" should be interpreted as inclusive of plural references unless the context clearly dictates otherwise.

[0024] "Acyl" refers to a group of formula -CO-R_x wherein R_x is H, or is optionally substituted alkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl. Examples of acyl groups include, for example, -CHO, -CO-Me, and -CO-Ph.

[0025] "Administering" or "administration of" a compound or composition drug to a patient (and grammatical equivalents of this phrase) refers to direct administration, which may be administration to a patient by a medical professional or may be self-administration, and/or indirect administration, which may be the act of prescribing a drug. For example, a physician who instructs a patient to self-administer a drug and/or provides a patient with a prescription for a drug is administering the drug to the patient.

[0026] "Alkoxy" refers to an alkyl group covalently bonded to an oxygen atom. In other words, an alkoxy group has the general structure -O-alkyl. C₁-C₆ alkoxy groups include, for example, methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, sec-butoxy, tert-butoxy, n-pentoxy, 2-pentoxy, 3-pentoxy, isopentoxy, neopentoxy, hexoxy, 2-hexoxy, 3-hexoxy, and 3-methylpentoxy.

[0027] "Alkenyl" refers to a straight (or linear) or branched chain hydrocarbon group containing at least one carbon-carbon double bond. C₁-C₆ alkenyl groups include, for example, vinyl, allyl, and butenyl.

[0028] "Alkyl" refers to a straight (or linear) or branched chain hydrocarbon group. C₁-C₆ alkyl groups include, for example, methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, pentyl, 2-pentyl, isopentyl, neopentyl, hexyl, 2-hexyl, 3-hexyl and 3-methylpentyl.

[0029] "Amino" refers to a monovalent radical -NR^aR^b wherein R^a and R^b are independently hydrogen, alkyl, aryl or heteroaryl. The term "alkylamino" refers to the group -NR^aR^b where R^a is alkyl and R^b is H or alkyl. For dialkylamino groups, the alkyl portions can be the same or different and can also be combined to form a 3- to 8-membered ring with the nitrogen atom to which each is attached. Accordingly, a group represented as -NR^aR^b is meant to include heterocyclyl groups such as piperidinyl, pyrrolidinyl, morpholinyl, azetidinyl and the like.

[0030] "Aryl" refers to a cyclic moiety that includes one or more monocyclic or fused ring aromatic systems containing from 6-20 ring carbon atoms. Such moieties include any moiety that has one or more monocyclic or bicyclic fused ring aromatic systems, including but not limited to phenyl and naphthyl.

[0031] "(C_m-C_n), C_m-C_n, or C_m-n" refer to the number of carbon atoms in a certain group before which one of these symbols are placed. For example, C₁-C₆ alkyl refers to an alkyl group containing from 1 to 6 carbon atoms.

[0032] "Carboxamide or carboxamido" refers to a monovalent radical -CO-NR^aR^b, wherein NR^aR^b is an "amino" group as defined above.

[0033] "Carrier" refers to a solid or liquid substance such as a polymer, solvent, suspending agent, absorbing agent, or adsorbing agent for the pre-delivery or capture of a compound of this invention for subsequent delivery. The carrier may be liquid or solid and is selected with the planned manner of administration in mind.

[0034] "Comprising" when used to define compounds, compositions and methods means that the recited elements may be present with other materials or steps. "Consisting essentially of," when used to define compounds, compositions

or methods, means that the recited elements may not be present with other elements that would materially affect the basic and novel characteristics of the claimed invention. "Consisting of," means only the recited elements. Embodiments defined by each of these transition terms are within the scope of this invention.

[0035] "Cycloalkyl" refers to, unless otherwise stated, cyclic versions of "alkyl", "alkenyl" and "alkynyl" in which all ring atoms are carbon. "Cycloalkyl" refers to a mono- or polycyclic group. "Cycloalkyl" may form a bridged ring or a spiro ring. The cycloalkyl group may have one or more double or triple bond(s). Typical cycloalkyl groups have from 3 to 8 ring atoms. Examples of cycloalkyl include cyclopentyl, cyclohexyl, 1-cyclohexenyl, 3-cyclohexenyl, and cycloheptyl.

[0036] "Halogen" or "halo" refers to by themselves or as part of another substituent, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom.

[0037] "Heteroaryl" refers to a monocyclic aromatic system having 5 or 6 ring atoms, or a fused ring bicyclic aromatic system having 8-20 atoms, in which the ring atoms are C, O, S, SO, SO₂, or N, and at least one of the ring atoms is a heteroatom, i.e., O, S, SO, SO₂, or N. Heteroaryl groups include, for example, acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothio-furanyl, benzothiophenyl, benzoxazolyl, benzothiazolyl, benzotriazolyl, benzotetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazolinyl, carbazolyl, NH-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, dithiazinyl, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, indazolyl, indolenyl, indolinyl, indolizinyl, indolyl, iso-benzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, oxazolidinyl, oxazolyl, oxazolidinyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxythiinyl, phenoxyazinyl, phthalazinyl, piperazinyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazoliny, pyrazolyl, pyridazinyl, pyridoxazolyl, pyridoimidazolyl, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolyl, quinazolinyl, quinolinyl, quinoxalinyl, quinuclidinyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, tetrazolyl, thiadiazinyl, thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl and xanthenyl. Unless indicated otherwise, the arrangement of the heteroatoms within the ring may be any arrangement allowed by the bonding characteristics of the constituent ring atoms.

[0038] "Heterocycl" or heterocyclic refers to a monocyclic or fused ring multi cyclic cycloalkyl group at least a portion of which is not aromatic and in which one or more of the carbon atoms in the ring system is replaced by a heteroatom selected from O, S, SO, SO₂, P, or N. Examples of heterocycl groups include but are not limited to imidazolinyl, morpholinyl, piperidinyl, piperidin-2-onyl, piperazinyl, pyrrolidinyl, pyrrolidine-2-onyl, tetrahydrofuranyl, tetrahydropyranyl, and tetrahydroimidazo [4,5-c] pyridinyl.

[0039] "Pharmaceutically acceptable salts" refers to salts of the active compounds which are prepared with relatively nontoxic acids or bases, depending on the particular acidic or basic nature of the compounds described herein. When compounds of the present invention contain relatively acidic functionalities, base addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired base, either neat or in a suitable inert solvent. Examples of salts derived from pharmaceutically-acceptable inorganic bases include aluminum, ammonium, calcium, lithium, magnesium, potassium, sodium, and the like. Salts derived from pharmaceutically-acceptable organic bases include salts of primary, secondary and tertiary amines, including substituted amines, cyclic amines, naturally-occurring amines and the like, such as arginine, betaine, caffeine, choline, diethylamine, 2- diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine and the like. When compounds of the present invention contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived from relatively nontoxic organic acids like acetic, propionic, isobutyric, malonic, benzoic, succinic, suberic, fumaric, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, methanesulfonic, and the like. Also included are salts of amino acids such as arginine and the like, and salts of organic acids like glucuronic or galactunoric acids. Certain specific compounds of the present invention may contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

[0040] "Pharmaceutically acceptable excipient, carrier, or diluent" refers to an excipient, carrier, or diluent that is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable, and includes an excipient, carrier, or diluent that is acceptable for human pharmaceutical use as well as veterinary use. A "pharmaceutically acceptable excipient, carrier, or diluent" includes both one and more than one such excipient, carrier, or diluent.

[0041] "Reduction" or "inhibition" of a symptom or symptoms (and grammatical equivalents of this phrase) of a pathological condition or disease refers to decreasing the severity or frequency of the symptom(s), or elimination of the symptom(s).

[0042] "Subject," used herein interchangeably with "individual" and "patient," refers to a vertebrate, typically a mammal,

and usually a human. Mammals include, but are not limited to, mice, rats, rabbits, simians, bovines, ovines, porcines, canines, felines, farm animals, sport animals, pets, equines, and primates.

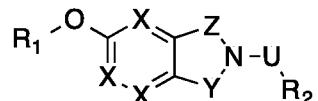
[0043] "Substituted" refers to a group as defined herein in which one or more bonds to a carbon(s) or hydrogen(s) are replaced by a bond to non-hydrogen and non-carbon atom "substituents" include, but are not limited to, a halogen atom; an oxygen atom in groups such as hydroxyl groups, alkoxy groups, aryloxy, and acyloxy groups; a sulfur atom in groups such as thiol groups, alkyl and aryl sulfide groups, sulfone groups, sulfonyl groups, and sulfoxide groups; a nitrogen atom in groups such as nitro, -NH₂, alkylamines, dialkylamines, arylamines, alkylarylamines, diarylamines, alkoxyamino, hydroxyamino, acylamino, sulfonylamino, N-oxides, imides, and enamines; and other heteroatoms in various other groups. "Substituents" also include groups in which one or more bonds to a carbon(s) or hydrogen(s) atom is replaced by a higher-order bond (e.g., a double- or triple-bond) to a heteroatom such as oxygen in oxo, acyl, amido, alkoxy carbonyl, aminocarbonyl, carboxyl, and ester groups; nitrogen in groups such as imines, oximes, hydrazones, and nitriles. "Substituents" further include groups in which one or more bonds to a carbon(s) or hydrogen(s) atoms is replaced by a bond to a cycloalkyl, heterocyclyl, aryl, and heteroaryl groups. For cycloalkyl, heterocyclyl, aryl, and heteroaryl groups, "substituents" still further include, substituted and unsubstituted alkyl groups. Other substituents include ethynyl, vinyl, carboxyl and its esters and amides, hydroxymethyl, and methyl. Another "substituent" is the trifluoromethyl or other fluoroalkyl group and other groups that contain these groups. Two substituents on same or adjacent carbon atoms may together with the carbon atoms to which they are bonded form a heterocyclic or cycloalkyl group. Typically, a particular group may have 0 (unsubstituted), 1, 2 or 3 substituents. As will be apparent to the skilled artisan, substitutions with substituents will not result in polymeric moieties of greater than 1000 molecular weight.

[0044] "Sulfonamide or sulfonamido" refers to a monovalent radical -SO₂-NR^aR^b, wherein NR^aR^b is an "amino" group as defined above.

[0045] "Therapeutically effective amount" is an amount administered to a patient with a disease mediated by GPR120 that is sufficient to effect beneficial or desired results. A therapeutically effective amount can be administered in one or more administrations, applications, or dosages.

[0046] "Treating" or "treatment of" a condition or patient refers to taking steps to obtain beneficial or desired results, including clinical results such as the reduction of symptoms. For purposes of this invention, beneficial or desired clinical results include, but are not limited to, alleviation or amelioration of one or more symptoms of diseases mediated by GPR120; diminishment of extent of such diseases; delay or slowing of such disease progression; amelioration, palliation, or stabilization of such diseases; or other beneficial results.

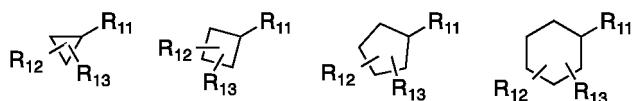
[0047] Accordingly, in a first aspect, the invention provides compounds of **Formula I**:

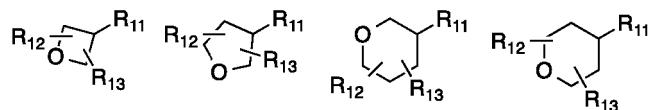


Formula I

or tautomers, isotopomers and stereoisomers thereof, and prodrugs of any of the foregoing, and pharmaceutically acceptable salts and solvates of all of the foregoing, wherein X is CH, CR₃, or N; Y is SO₂ Z is -CH₂-, -CH(CH₃)-, -C(CH₃)₂-, -C(CH₂CH₃)-, - (CO)CH₂-, or -CHCH-; U is CH₂, -CH(CH₃)-, -C(CH₃)₂-, or -CH₂CH₂-, R₁ is an optionally substituted alkyl group, an optionally substituted 3-7 membered cycloalkyl or heterocyclyl group, an optionally substituted 6-membered aryl group, an optionally substituted 5- or 6-membered heteroaryl group, an optionally substituted 5,6- or 6,6-bicyclic heteroaryl group, or an optionally substituted bicyclic aryl group; R₂ is an optionally substituted 3-7 membered cycloalkyl or heterocyclyl group, an optionally substituted 6-membered aryl group, an optionally substituted 5- or 6-membered heteroaryl group, or an optionally substituted 5,6- or 6,6-bicyclic heteroaryl group, or an optionally substituted aryl group; R₃ is a halogen, or an optionally substituted alkyl or alkoxy group. In one embodiment, R₂ is a non-hydrogen substituent.

[0048] In a preferred embodiment, R₁ is an optionally substituted cycloalkyl or heterocyclyl group. Examples of specific preferred cycloalkyl and heterocyclyl groups are shown below wherein R₁₁ is the attachment point to the core scaffold. R₁₂ and R₁₃ are independently H, CH₃, CF₃, or F.

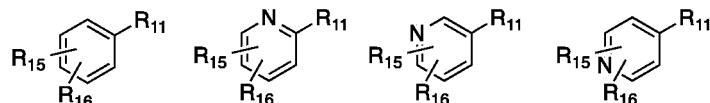




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[0049] In another preferred embodiment, R₁ is an optionally substituted aryl or heteroaryl group. Examples of specific preferred aryl and heteroaryl groups are shown below wherein R₁₁ is the attachment point to the core scaffold, R₁₅ is H, halogen, alkyl, CF₃, OCH₃, OCF₃, or CN, and R₁₆ is H, halogen, alkyl, CF₃, OCH₃, OCF₃, CN, NHCOR₁₄, or N(CH₃)COR₁₄ wherein R₁₄ is alkyl, cycloalkyl, aryl or heteroaryl.

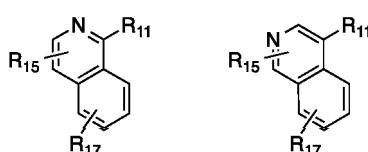
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[0050] In another preferred embodiment, R₁ is an optionally substituted fused bicyclic group. Examples of specific preferred fused bicyclic groups are shown below wherein R₁₁ is the attachment point to the core scaffold, and R₁₅ and R₁₇ are independently H, halogen, alkyl, CF₃, OCH₃, OCF₃, or CN.

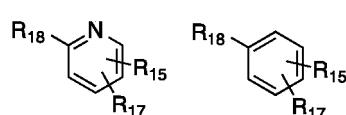
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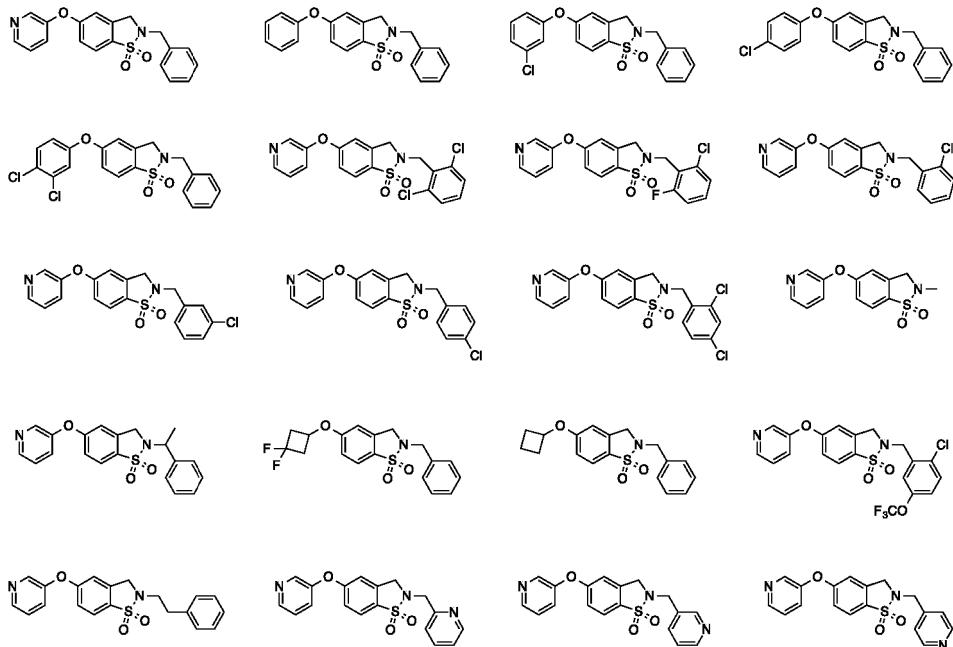
[0051] In another preferred embodiment, U is CH₂, and R₂ is an optionally substituted 5 or 6-membered aryl or heteroaryl group, wherein R₁₈ is the attachment point to U, and R₁₅ and R₁₇ are independently H, halogen, alkyl, CF₃, OCH₃, OCF₃, or CN.

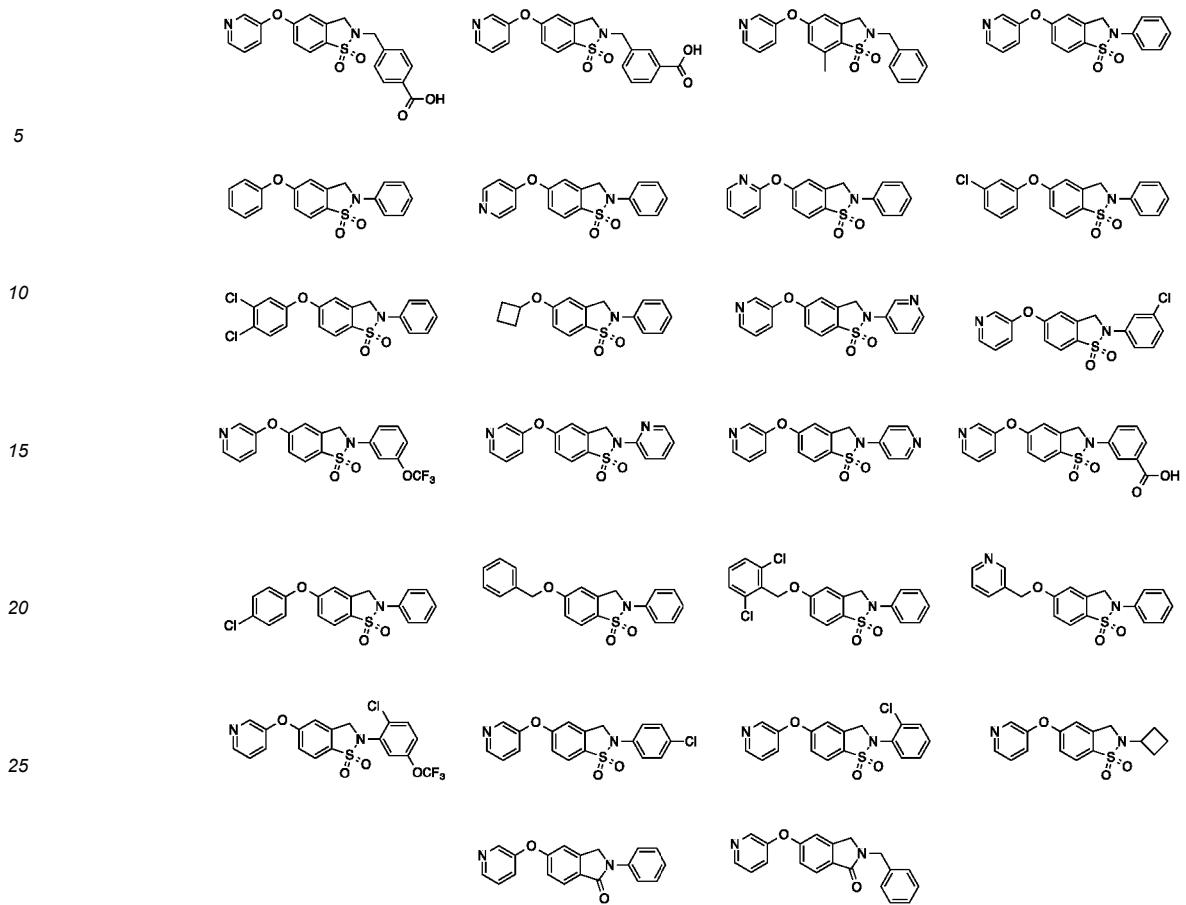
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[0052] In another aspect, a compound provided herein is selected from:





[0053] Certain compounds of the present invention are synthesized as schematically described herein below. Other compounds of the present invention can be synthesized by adapting these and other methods exemplified in the Examples section below or methods known to one of skill in the art upon appropriate substitution of starting materials, other reagents, and/or process conditions (i.e., reaction temperatures, times, mole ratios of reactants, solvents, pressures, and the like).

[0054] For compounds of the invention that contain one or more chiral centers, such compounds can be prepared or isolated as pure stereoisomers, i.e., as individual enantiomers or diastereomers, or as stereoisomer-enriched mixtures. All such stereoisomers (and enriched mixtures) are included within the scope of the compounds provided and utilized herein unless otherwise indicated. Pure stereoisomers (or enriched mixtures) may be prepared using, for example, optically active starting materials or stereoselective reagents well-known in the art. Alternatively, racemic mixtures of such compounds can be separated using, for example, chiral column chromatography, chiral resolving agents and the like.

[0055] In another aspect, the present invention provides compositions comprising a compound of the present invention, and at least one pharmaceutically acceptable excipient, i.e., pharmaceutical formulations. In general, the compounds of the present invention can be formulated for administration to a patient by any of the accepted modes of administration. Thus, the invention provides solid and liquid formulations of the compounds of the invention. Various formulations and drug delivery systems are available in the art. See, e.g., Gennaro, A.R., ed. (1995) Remington's Pharmaceutical Sciences, 18th ed., Mack Publishing Co..

[0056] Typically, compounds of the present invention will be administered as pharmaceutical compositions by one of the following routes: oral, systemic (e.g., transdermal, intranasal or by suppository), or parenteral (e.g., intramuscular, intravenous or subcutaneous) administration. Compositions can take the form of tablets, pills, capsules, semisolids, powders, sustained release formulations, solutions, suspensions, elixirs, aerosols, or any other appropriate compositions.

[0057] Pharmaceutical dosage forms of a compound of the present invention may be manufactured by any of the methods well-known in the art, such as, for example, by conventional mixing, sieving, dissolving, melting, granulating, dragee-making, tabletting, suspending, extruding, spray-drying, levigating, emulsifying, (nano/micro-) encapsulating, entrapping, or lyophilization processes. As noted above, the compositions of the present invention can include one or more physiologically acceptable inactive ingredients that facilitate processing of active molecules into preparations for pharmaceutical use.

[0058] Pharmaceutical formulations have been developed especially for drugs that show poor bioavailability based upon the principle that bioavailability can be increased by increasing the surface area i.e., decreasing particle size. For

example, U.S. Pat. No. 4,107,288 describes a pharmaceutical formulation having particles in the size range from 10 to 1,000 nm in which the active material is supported on a crosslinked matrix of macromolecules. U.S. Patent No. 5,145,684 describes the production of a pharmaceutical formulation in which the drug substance is pulverized to nanoparticles (average particle size of 400 nm) in the presence of a surface modifier and then dispersed in a liquid medium to give a pharmaceutical formulation that exhibits remarkably high bioavailability. In some embodiments, the compounds of the present invention are formulated accordingly.

[0059] The compositions are comprised in general, a compound of the present invention in combination with at least one pharmaceutically acceptable excipient. Acceptable excipients are non-toxic, aid administration, and do not adversely affect the therapeutic benefit of the claimed compounds. Such excipient may be any solid, liquid, semi-solid or, in the case of an aerosol composition, gaseous excipient that is generally available to one of skill in the art.

[0060] Solid pharmaceutical excipients include starch, cellulose, talc, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, magnesium stearate, sodium stearate, glycerol monostearate, sodium chloride, dried skim milk and the like. Liquid and semisolid excipients may be selected from glycerol, propylene glycol, water, ethanol and various oils, including those of petroleum, animal, vegetable or synthetic origin, e.g., peanut oil, soybean oil, mineral oil, sesame oil, etc. Preferred liquid carriers, particularly for injectable solutions, include water, saline, aqueous dextrose, and glycals. Other suitable pharmaceutical excipients and their formulations are described in Remington's Pharmaceutical Sciences, edited by E. W. Martin (Mack Publishing Company, 18th ed., 1990).

[0061] The present compositions may, if desired, be presented in a pack or dispenser device containing one or more unit dosage forms containing the active ingredient. Such a pack or device may, for example, comprise metal or plastic foil, such as a blister pack, or glass, and rubber stoppers such as in vials. The pack or dispenser device may be accompanied by instructions for administration. Compositions comprising a compound of the invention formulated in a compatible pharmaceutical carrier may also be prepared, placed in an appropriate container, and labeled for treatment of an indicated condition.

[0062] The amount of the compound in a formulation can vary within the full range employed by those skilled in the art. Typically, the formulation will contain, on a weight percent (wt %) basis, from about 0.01-99.99 wt % of a compound of the present invention based on the total formulation, with the balance being one or more suitable pharmaceutical excipients. Generally, the compound is present at a level of about 1-80 wt %.

[0063] In another aspect, the invention provides a method of producing a therapeutic effect of GPR120 by contacting a therapeutically effective amount of a compound or a composition of the present invention with the GPR120 in need thereof. In one embodiment, the therapeutic effect is produced in a cell. In another embodiment, the contacting is performed *in vitro* or *in vivo*.

[0064] In another aspect, provided herein is a method of treating Type 2 diabetes in a subject in need thereof comprising administering to the subject a therapeutically effective amount of a compound or a composition of the present invention. In one embodiment, the subject is a human.

[0065] The invention having been described in summary and in detail is illustrated and not limited by the examples below. Examples 1-46 illustrate specific compounds of the invention and methods for their synthesis. Examples 47 and 48 illustrate methods whereby the ability of compounds of the invention to activate the GPR120 receptor can be measured in biological assays.

40 SYNTHESES EXAMPLES

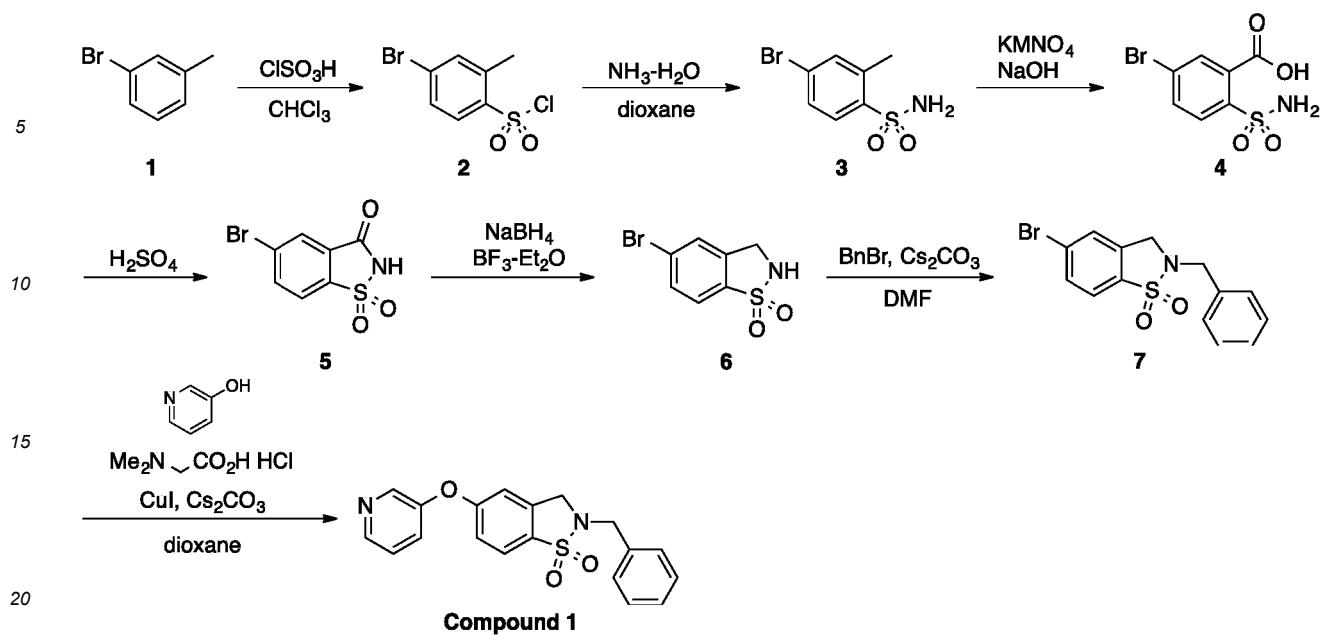
Example 1

Synthesis of Compound 1

45 **[0066]**

50

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Step 1.

[0067] To a solution of **1** (50.0 g, 292 mmol) stirred in CHCl_3 (500 mL) was added chlorosulfuric acid (238 g, 2.05 mol) at 0°C. The reaction mixture was stirred at 0°C for 0.5 h. When TLC showed the reaction was complete, the reaction mixture was poured into ice water (500 mL), extracted by CH_2Cl_2 (3×500 mL), dried over anhydrous Na_2SO_4 , and concentrated. The crude material was washed with petroleum ether (20 mL) to afford **2** (49.2 g, 59%).

Step 2.

[0068] To a solution of **2** (40.0 g, 148 mmol) stirred in dioxane (800 mL) was added $\text{NH}_3\text{-H}_2\text{O}$ (1.5 L, 15.58 mol) at 0°C. The reaction mixture was stirred at 0°C for 1 h. When TLC showed the reaction was complete, the reaction mixture was extracted with CH_2Cl_2 (6×500 mL), dried over anhydrous Na_2SO_4 , and concentrated. The crude material was washed with petroleum ether (100 mL) to afford **3** (36 g, 92% yield).

Step 3.

[0069] To a solution of NaOH (24.0 g, 600 mmol) in H_2O (240 mL) at 0°C was added **3** (30.0 g, 120 mmol) and KMnO_4 (94.8 g, 600 mmol) portionwise. The reaction mixture was stirred at 60°C for 12 h under N_2 . When LCMS showed the reaction was complete, the reaction mixture was quenched by Na_2SO_3 (30 g) at 0°C and filtered. The filtrate was acidified to pH=2 and filtered to afford **4** (25.0 g) as a solid which was used without further purification.

Step 4.

[0070] To concentrated H_2SO_4 (100 mL) was added **4** (10.0 g, 35.7 mmol) at 0°C and the reaction mixture was stirred at 40°C for 12 h. When LCMS showed the reaction was complete, the reaction mixture was poured into ice water (200 mL) and then extracted by ethyl acetate (3×200 mL). The organic layer was washed with H_2O (3×20 mL), dried over anhydrous Na_2SO_4 , and concentrated to afford **5** (9.1 g).

Step 5.

[0071] To a solution of **5** (9.1 g, 34.7 mmol) stirred in THF (200 mL) was added NaBH_4 (13.1 g, 347 mmol) and $\text{BF}_3\text{-Et}_2\text{O}$ (49.3 g, 347 mmol) portionwise at 0°C. The reaction mixture was stirred at 70°C for 12 h under N_2 . When LCMS showed the reaction was complete, the reaction mixture was poured into ice water (250 mL) and extracted with ethyl acetate (3×200 mL). The organic layer was washed with H_2O (100 mL), dried over anhydrous Na_2SO_4 , and concentrated to afford **6** (8.6 g).

Step 6.

[0072] To a solution of **6** (50 mg, 0.20 mmol) and benzyl bromide (52 mg, 0.30 mmol) in DMF (2 mL) was added cesium carbonate (197 mg, 0.60 mmol). The reaction mixture was stirred 12 h at room temperature under an inert atmosphere. Upon completion, the reaction mixture was concentrated under reduced pressure and purified by prep-TLC to afford **7** (30 mg).

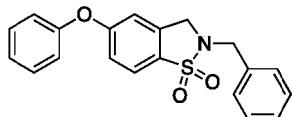
Step 7.

[0073] To a solution of **7** (31 mg, 0.092 mmol) and pyridin-3-ol (8.8 mg, 0.092 mmol) in dioxane (2 mL) was added cesium carbonate (90 mg, 0.028 mmol), Cul (7 mg, 0.037 mmol), and 2-(dimethylamino)acetic acid hydrochloride (2.6 mg, 0.018 mmol). The reaction mixture was stirred at 90°C under inert atmosphere for 12 h. Upon completion, the reaction was concentrated and purified by prep-HPLC (0.04%HCl/CH₃CN/H₂O system) to afford **Compound 1** (10 mg, 31%) as a white solid. **1H NMR** (CD₃OD, 400MHz) δ 8.26-8.24 (d, 1H), 8.07-7.95 (s, 1H), 7.96-7.93 (d, 1H), 7.45-7.32 (m, 2H), 4.43 (s, 2H), 4.28 (s, 2H); **LCMS** (ESI): m/z 353.0 (M+H).

Example 2

Synthesis of Compound 2

[0074]

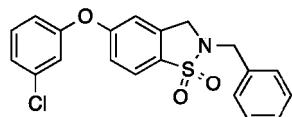


[0075] **Compound 2** was prepared in a manner similar to **Compound 1**. **1H NMR** (DMSO-*d*₆, 400MHz) δ 7.91-7.89 (d, 1H), 7.45-7.38 (m, 7H), 7.25-7.23 (m, 1H), 7.14-7.10 (m, 4H), 4.36 (s, 2H), 4.24 (s, 2H); **LCMS** (ESI): m/z 352.0 (M+H).

Example 3

Synthesis of Compound 3

[0076]

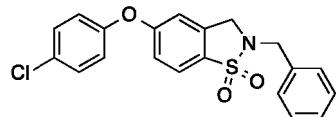


[0077] **Example 3** was prepared in a manner similar to **Compound 1**. **1H NMR** (DMSO-*d*₆, 400MHz) δ 7.82-7.80 (d, 1H), 7.44-7.43 (d, 2H), 7.39-7.35 (m, 4H), 7.21-7.20 (m, 2H), 7.13-7.12 (d, 1H), 7.04-7.02 (m, 2H), 4.40 (s, 2H), 4.21 (s, 2H); **LCMS** (ESI): m/z 386.0 (M+H).

Example 4

Synthesis of Compound 4

[0078]



[0079] **Compound 4** was prepared in a manner similar to **Compound 1**. **1H NMR** (DMSO-*d*₆, 400MHz) δ 7.80-7.78 (d, 1H), 7.44-7.31 (m, 7H), 7.19-7.18 (d, 1H), 7.08-7.06 (d, 2H), 7.01 (s, 1H), 4.39 (s, 2H), 4.20 (s, 2H); **LCMS** (ESI):

50 m/z 386.0 (M+H).

Example 5

5 Synthesis of Compound 5

[0080]



15 [0081] Compound 5 was prepared in a manner similar to Compound 1. **1H NMR** (DMSO-*d*₆, 400MHz) δ 7.94-7.92 (d, 1H), 7.69-7.67 (d, 1H), 7.51-7.50 (d, 1H), 7.42-7.40 (m, 5H), 7.39-7.37 (d, 1H), 7.27 (s, 1H), 7.20-7.16 (d, 1H), 4.37 (s, 2H), 4.24 (s, 2H); **LCMS** (ESI): m/z 420.0 (M+H).

Example 6

20 Synthesis of Compound 6

[0082]



30 [0083] Compound 6 was prepared in a manner similar to Compound 1. **1H NMR** (DMSO-*d*₆, 400MHz) δ 7.93-7.90 (d, 1H), 7.68-7.66 (d, 1H), 7.56-7.54 (m, 3H), 7.45-7.43 (m, 2H), 7.39-7.26 (m, 1H), 4.58 (s, 2H), 4.32 (s, 2H); **LCMS** (ESI): m/z 421.0 (M+H).

Example 7

35 Synthesis of Compound 7

[0084]



45 [0085] Compound 7 was prepared in a manner similar to Compound 1. **1H NMR** (CD₃OD, 400MHz) δ 8.79-8.68 (d, 1H), 8.28-8.26 (d, 1H), 8.06-8.04 (m, 1H), 7.92-7.90 (d, 1H), 7.43-7.32 (m, 4H), 7.20-7.15 (m, 1H), 4.61 (s, 2H), 4.42 (s, 2H); **LCMS** (ESI): m/z 405.0 (M+H).

Example 8

50 Synthesis of Compound 8

[0086]

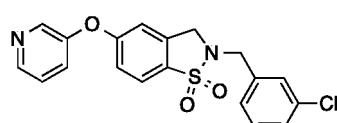


[0087] Compound 8 was prepared in a manner similar to Compound 1. **1H NMR** (DMSO-*d*₆ 400MHz) δ 8.52-8.48 (t, 2H), 7.95-7.67 (m, 1H), 7.53-7.51 (m, 1H), 7.39-7.28 (m, 1H), 7.28-7.20 (m, 1H), 4.48 (s, 2H), 4.37 (s, 2H); **LCMS** (ESI): m/z 387.0 (M+H).

5 **Example 9**

Synthesis of Compound 9

10 **[0088]**

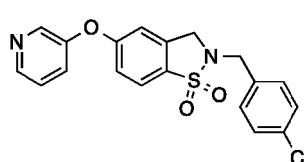


15 [0089] Compound 9 was prepared in a manner similar to Compound 1. **1H NMR** (CD₃OD, 400MHz) δ 8.81-8.69 (d, 2H), 8.31-8.29 (d, 1H), 8.10-8.08 (m, 1H), 7.97-7.95 (d, 1H), 7.49-7.44 (m, 2H), 7.39-7.33 (m, 4H), 4.45 (s, 2H), 4.33 (s, 2H); **LCMS** (ESI): m/z 387.0 (M+H).

20 **Example 10**

Synthesis of Compound 10

25 **[0090]**

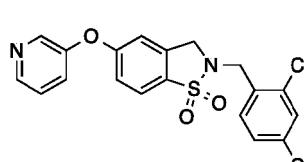


30 [0091] Compound 10 was prepared in a manner similar to Compound 1. **1H NMR** (CD₃OD, 400MHz) δ 8.82 (s, 1H), 8.70 (s, 1H), 8.34-8.32 (d, 1H), 8.11-8.08 (m, 1H), 7.96-7.94 (d, 1H), 7.46-7.36 (m, 6H), 4.43 (s, 2H), 4.31 (s, 2H); **LCMS** (ESI): m/z 387.0 (M+H).

35 **Example 11**

Synthesis of Compound 11

40 **[0092]**

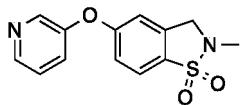


45 [0093] Compound 11 was prepared in a manner similar to Compound 1. **1H NMR** (CD₃OD, 400MHz) δ 8.55-8.49 (m, 2H), 7.95 (d, 1H), 7.69 (bs, 2H), 7.60-7.53 (m, 2H), 7.51-7.47 (m, 1H), 7.28 (d, 1H), 7.20 (s, 1H), 4.47 (s, 2H), 4.38 (s, 2H); **LCMS** (ESI): m/z 421.0 (M+H).

Example 12

Synthesis of Compound 12

55 **[0094]**



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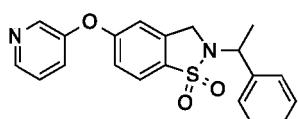
[0095] Compound 12 was prepared in a manner similar to Compound 1. **1H NMR** (CD_3OD , 400MHz) δ 8.82 (s, 1H), 8.70-8.68 (d, 1H), 8.36-8.33 (d, 1H), 8.12-8.10 (d, 1H), 7.44-7.40 (m, 2H), 4.40 (s, 2H), 2.90 (s, 3H); **LCMS** (ESI): m/z 277.0 (M^+).

10 Example 13

Synthesis of Compound 13

[0096]

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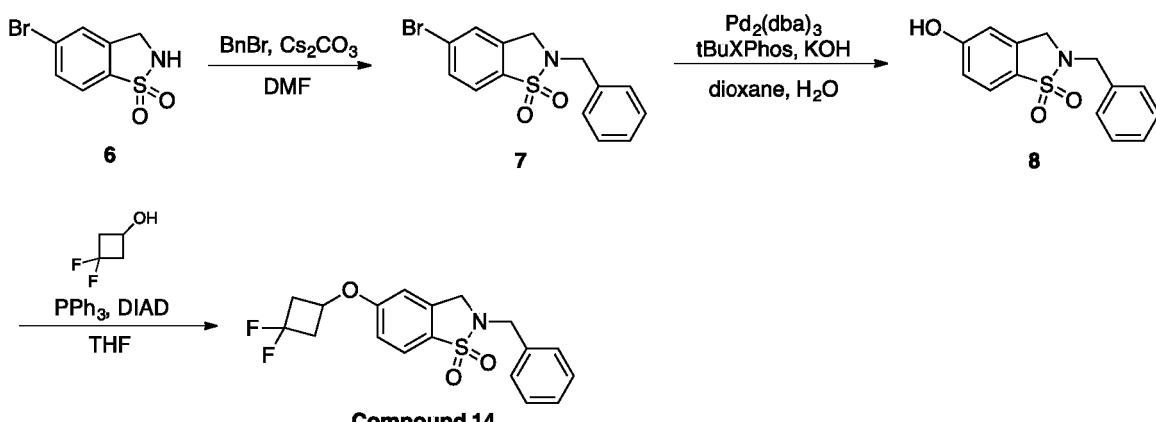
[0097] Compound 13 was prepared in a manner similar to Compound 1. **¹H NMR** (CD_3OD , 400MHz) δ 8.78 (d, 2H), 8.27-8.25 (d, 2H), 7.92-7.90 (d, 1H), 7.49-7.47 (d, 1H), 7.38-7.29 (m, 8H), 4.96-4.93 (m, 1H), 4.36-4.32 (d, 1H), 4.06-4.02 (d, 1H), 1.79-1.77 (d, 3H); **LCMS** (ESI): m/z 367.0 (M+H).

25 Example 14

Synthesis of Compound 14

[0098]

30



45

Step 1

[0099] To a solution of **6** (1.0 g, 4.03 mmol) in DMF (15 mL) was added Cs₂CO₃ (2.63 g, 8.06 mmol) and benzyl bromide (1.03 g, 6.05 mmol). The mixture was stirred at 30°C for 12 hours and then filtered. The filtrate was concentrated under reduced pressure to give a residue, which was diluted with water (80 mL) and extracted with CH₂Cl₂ (3 × 60 mL). The combined organic layers were washed with water (3 × 60 mL) and brine (2 × 80 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to afford **7** (1.2 g) as a white solid which was used directly in the next step without purification.

5

[0100] A mixture of 7 (120 mg crude material), $\text{Pd}_2(\text{dba})_3$ (65 mg, 0.071 mmol), t-Bu Xphos (30 mg, 0.071 mmol) and KOH (99.5 mg, 1.77 mmol) in dioxane (2 mL) and H_2O (2 mL) was degassed, purged with N_2 (3X), and then stirred at

85°C for 12 hours. The reaction mixture was concentrated under reduced pressure to give a residue that was diluted with water (5 mL). The solution was adjusted to pH = 3 using 2M HCl and then extracted with ethyl acetate (3 × 15 mL). The organic layer was washed with brine (2 × 20 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to give **8** (130 mg) as a yellow solid which was used directly in the next step without purification.

5

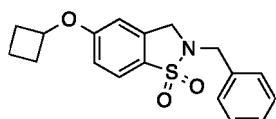
Step 3.

[0101] A solution of **8** (50 mg, 0.18 mmol), 3,3-difluorocyclobutanol (23.6 mg, 0.22 mmol), PPh_3 (95 mg, 0.36 mmol) and DIAD (74 mg, 0.36 mmol) was stirred in THF (2 mL) at 35°C under N_2 for 12 hours. When LCMS showed the reaction was complete, the reaction mixture was concentrated to give a residue. The residue was purified by prep-HPLC (0.04% HCl/ACN/H₂O system) to give **Compound 14** (14 mg, 21%) as a white solid. **1H NMR** (CD_3OD , 400MHz) δ 7.74-7.46 (d, 1H), 7.44-7.38 (d, 2H), 7.36-7.32 (m, 2H), 7.11-7.09 (d, 1H), 6.93 (s, 1H), 4.80 (s, 2H), 4.21 (s, 2H), 3.31-3.12 (m, 2H), 2.76-2.69 (m, 2H); **LCMS** (ESI): m/z 366.0 (M+H).

15 **Example 15**

Synthesis of Compound 15

20 [0102]

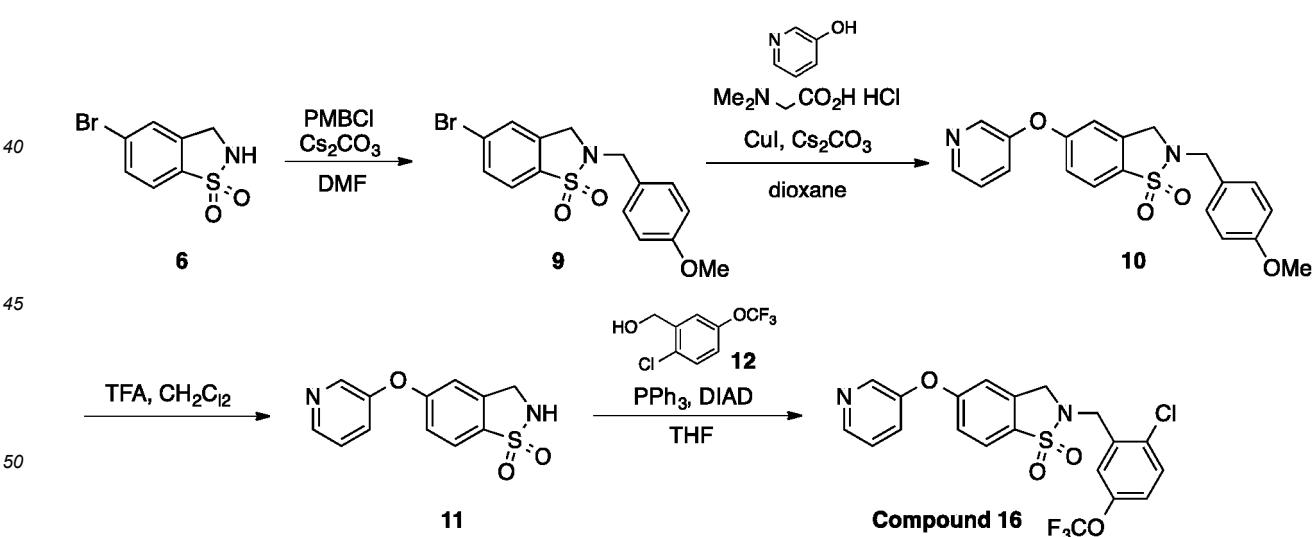


[0103] **Compound 15** was prepared in a manner similar to **Compound 14**. **1H NMR** ($\text{DMSO}-d_6$, 400MHz) δ 7.79-7.76 (d, 1H), 7.43-7.37 (m, 4H), 7.34-7.33 (m, 1H), 7.04-7.02 (m, 1H), 6.98 (s, 1H), 4.77-4.70 (m, 1H), 4.34 (s, 2H), 4.21 (s, 2H), 2.50-2.43 (m, 2H), 2.05-2.00 (m, 2H), 1.79-1.77 (m, 1H), 1.61-1.64 (m, 1H); **LCMS** (ESI): m/z 330.1 (M+H).

30 **Example 16**

Synthesis of Compound 16

35 [0104]



Step 1.

[0105] To a solution of **6** (300 mg, 1.21 mmol) and PMBCl (284 mg, 1.81 mmol) stirred in DMF (2. mL) was added Cs_2CO_3 (788 mg, 2.42 mmol). The reaction mixture was stirred at 35°C for 12 h. When LCMS showed the reaction was complete, the reaction mixture was quenched by H_2O (10 mL) and extracted with ethyl acetate (3 × 20 mL). The organic

layer was washed with H_2O (3×20 mL), dried over anhydrous Na_2SO_4 , concentrated, and purified by prep-TLC (petroleum ether : ethyl acetate = 1:1) to afford **9** (335 mg, 64%).

Step 2.

[0106] To a solution of **9** (1.50 g, 4.07 mmol) and pyridin-3-ol (775 mg, 8.15 mmol) stirred in dioxane (15 mL) was added CuI (620 mg, 3.26 mmol), Cs_2CO_3 (3.32 g, 10.2 mmol) and 2-(dimethylamino)acetic acid hydrochloride (227 mg, 1.63 mmol). The reaction mixture was stirred at 100°C under N_2 for 12 h. When LCMS showed the reaction was complete, the reaction mixture was filtered. The filtrate was concentrated and purified by prep-TLC (petroleum ether : ethyl acetate = 1:1.5) to afford **10** (770 mg, 42%) as a liquid.

Step 3.

[0107] A solution of **10** (770 mg, 2.01 mmol) stirred in TFA / CH_2Cl_2 (77 mL) at 25°C 12 h. When LCMS showed that the reaction was complete, the reaction mixture was concentrated. The crude material was dissolved in methyl-t-butylether (15 mL) and H_2O (10 mL). The water layer was adjusted to $\text{pH} = 10$ and concentrated. The solid was washed by CH_2Cl_2 : $\text{MeOH} = 10:1$ (30 mL) to produce **11** (500 mg, 76%) as a solid. **LCMS** (ESI): m/z 263.1. ($\text{M}+\text{H}$).

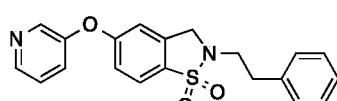
Step 4.

[0108] To a solution of **11** (80 mg, 0.31 mmol), **12** (69 mg, 31 mmol) and PPh_3 (80 mg, 0.31 mmol) stirred in THF (2 mL) was added DIAD (62 mg, 0.31 mmol). The reaction mixture was stirred at 40°C under N_2 for 12 h. When LCMS showed the reaction was complete, the reaction mixture was concentrated. The crude material was purified by prep-HPLC to afford **Compound 16** (8.7 mg, 6%). **1H NMR** (CD_3OD 400MHz) δ 8.443 (s, 2H), 7.87-7.85 (d, 1H), 7.85-7.67 (d, 1H), 7.64-7.57 (m, 3H), 7.50-7.29 (d, 2H), 4.59 (s, 2H), 4.42 (s, 2H); **LCMS** (ESI): m/z 471.1 ($\text{M}+\text{H}$).

Example 17

Synthesis of Compound 17

[0109]

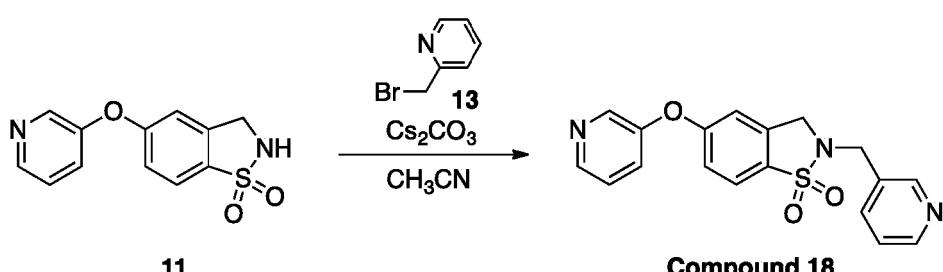


[0110] **Compound 17** was prepared in a manner similar to **Compound 16**. **1H NMR** (CD_3OD , 400MHz) δ 7.83-7.81 (d, 2H), 7.33-7.28 (s, 6H), 7.22-7.21 (m, 2H), 4.34 (d, 2H), 3.51-3.48 (m, 2H), 3.05-3.01 (s, 2H); **LCMS** (ESI): m/z 367.1 ($\text{M}+\text{H}$).

Example 18

Synthesis of Compound 18

[0111]



[0112] To a solution of **11** (80 mg, 0.18 mmol) in CH_3CN (3 mL) was added Cs_2CO_3 (149 mg, 0.46 mmol) and **13** (38

mg, 0.22 mmol). The mixture was stirred at 20°C for 2 hours and then filtered. The filtrate was concentrated under reduced pressure to give a residue which was purified by prep-HPLC (HCl, 0.05%HCl-ACN) to afford **Compound 18** (24 mg, 36% yield) as a yellow oil. **1H NMR** (CD_3OD , 400MHz) δ 8.86-8.85 (d, 2H), 8.72-8.71 (d, 1H), 8.67-8.65 (m, 1H), 8.24-8.22 (d, 1H), 8.14-8.12 (m, 1H), 8.05-7.99 (m, 2H), 8.01-7.99 (d, 1H), 7.48-7.51 (m, 2H), 4.99 (s, 2H), 4.70 (s, 2H); **LCMS** (ESI): m/z 354.0 (M+H).

5

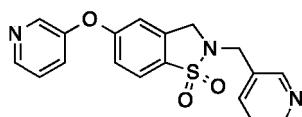
Example 19

Synthesis of Compound 19

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[0113]

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[0114] **Compound 19** was prepared in a manner similar to **Compound 18**. **1H NMR** (CD_3OD , 400MHz) δ 9.01 (s, 1H), 8.88-8.87 (d, 2H), 8.80-8.78 (d, 1H), 8.73-8.72 (d, 1H), 8.40-8.38 (d, 1H), 8.18-8.12 (m, 2H), 7.99-7.97 (d, 1H), 7.51-7.46 (m, 2H), 4.81 (s, 2H), 4.59 (s, 2H); **LCMS** (ESI): m/z 354.0 (M+H).

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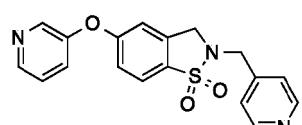
Example 20

Synthesis of Compound 20

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[0115]

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[0116] **Compound 20** was prepared in a manner similar to **Compound 18**. **1H NMR** (CD_3OD , 400MHz) δ 8.88-8.87 (m, 3H), 8.72-8.71 (d, 1H), 8.40-8.38 (d, 1H), 8.22-8.21 (d, 2H), 8.15-8.11 (m, 1H), 8.01-7.99 (d, 1H), 7.51-7.47 (m, 2H), 4.90 (s, 2H), 4.62 (s, 2H); **LCMS** (ESI): m/z 354.0 (M+H).

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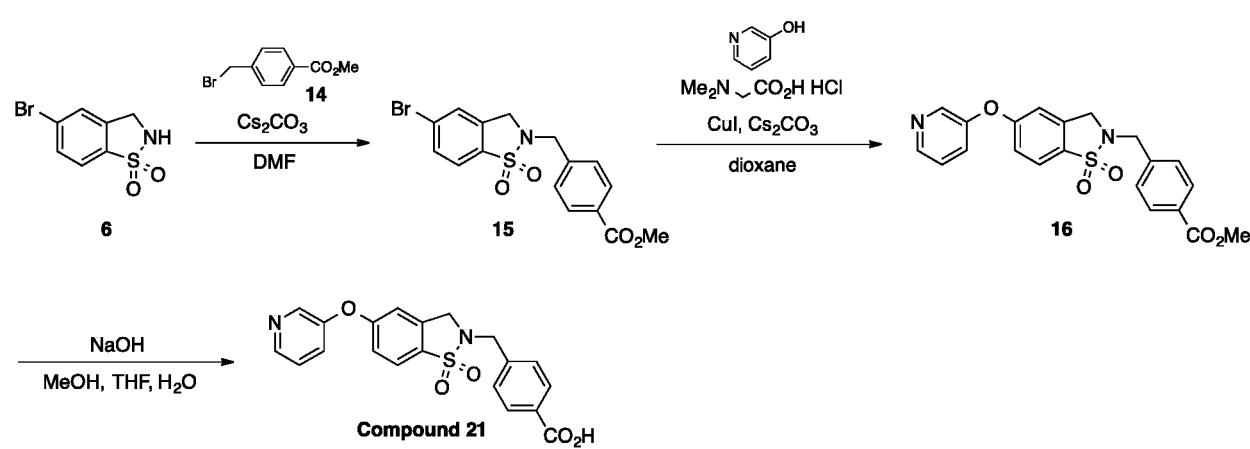
Example 21

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Synthesis of Compound 21

[0117]

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Step 1.

[0118] A mixture of **6** (150 mg, 0.60 mmol), **14** (180 mg, 0.79 mmol), Cs_2CO_3 (393 mg, 1.21 mmol) in DMF (2 mL) was degassed, purged with N_2 (3X), and then stirred at 35°C for 12 h. When the reaction was complete by LC-MS, it was filtered and diluted with ethyl acetate (30 mL). The organic layer was washed with water (3 × 30 mL) and brine (30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The crude material (180 mg, white solid) was used directly for next step without purification.

Step 2.

[0119] A mixture of **15** (180 mg, 0.27 mmol), pyridin-3-ol (33 mg, 0.35 mmol), CuI (15 mg, 0.08 mmol), Cs_2CO_3 (174 mg, 0.53 mmol) and 2-(dimethylamino)acetic acid hydrochloride (11 mg, 0.08 mmol) in dioxane (2 mL) was degassed, purged with N_2 (3X), and then stirred at 100°C for 24 hours. The reaction mixture was cooled, diluted with water (20 mL), and extracted with ethyl acetate (3 × 10 mL). The combined organic layer was washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The crude material was purified by prep-TLC (petroleum ether : ethyl acetate = 1:1) to provide **16** (80 mg, 0.15 mmol) as a light yellow oil.

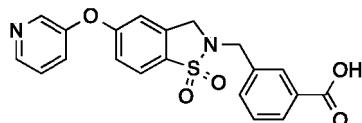
Step 3.

[0120] To a solution of **16** (80 mg, 0.15 mmol) in THF (1 mL) and MeOH (1 mL) was added NaOH (1 mL, 2M). The mixture was stirred at 15°C for 0.5 h, diluted with water (30 mL), and then acidified with 2N HCl (aq) to pH = 6. The solution was extracted with ethyl acetate (3 × 10 mL); the organic layer was washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The crude material was purified by prep-HPLC to give **Compound 21** (8.9 mg, 13%) as a white solid. **1H NMR** (DMSO-*d*₆, 400MHz) δ 8.54 (d, 2H), 7.99-7.93 (m, 3H), 7.73 (d, 1H), 7.61-7.50 (m, 3H), 7.29 (d, 1H), 7.21 (s, 1H), 4.47 (s, 2H), 4.30 (s, 2H).

Example 22

Synthesis of Compound 22

[0121]



[0122] **Compound 22** was prepared in a manner similar to **Compound 21**. **1H NMR** (DMSO-*d*₆, 400MHz) δ 8.58 (s, 2H), 8.02-7.94 (m, 2H), 7.90 (d, 1H), 7.78 (d, 1H), 7.70-7.60 (m, 2H), 7.56-7.48 (m, 1H), 7.30 (d, 1H), 7.22 (s, 1H), 4.47 (s, 2H), 4.28 (s, 2H); **LCMS** (ESI): m/z 397.0 (M+H).

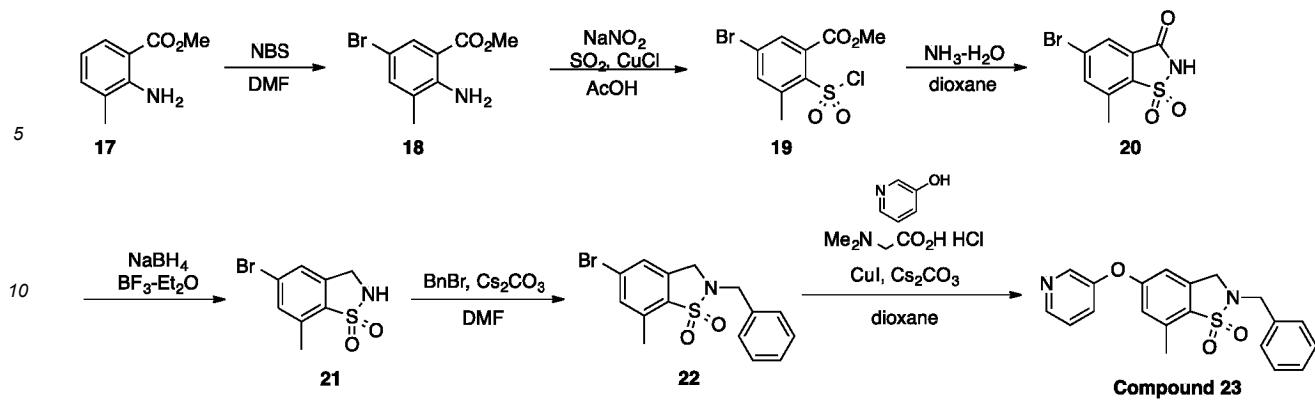
Example 23

45 Synthesis of Compound 23

[0123]

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15 Step 1.

[0124] To a solution of **17** (15.0 g, 90.8 mmol) in DMF (200 mL) was added NBS (16.2 g, 90.8 mmol) at 0°C. After addition, the mixture was warmed to 15°C and stirred for 14 hours. The reaction mixture was quenched by addition of water (200 mL) and then extracted with ethyl acetate (3 \times 250 mL). The combined organic phase was washed with water (3 \times 250 mL) and brine (2 \times 200 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated *in vacuo* to give **18** (21.0 g) as a gray solid which was used directly in the next transformation. **1H NMR** (CDCl_3 , 400MHz) δ 7.90-7.89 (d, 1H), 7.29-7.28 (d, 1H), 5.84 (s, 2H), 3.87 (s, 3H), 2.15 (s, 3H); **LCMS** (ESI): m/z 246.0 (M+H).

25 Step 2.

[0125] To a solution of **18** (11.0 g) in HCl (120 mL) and AcOH (20 mL) was added drop wise NaNO_2 (3.42 g, 49.6 mmol) in H_2O (20 mL) at 0°C. The mixture was stirred at 0°C for 30 minutes and then SO_2 (17.3 g, 270 mmol) and CuCl (1.34 g, 13.5 mmol) in AcOH (200 mL) was added portion wise. After 30 minutes at 0°C, the reaction mixture was poured into water (300 mL) and extracted with CH_2Cl_2 (3 \times 300 mL). The organic layer was washed with saturated brine (2 \times 300 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to give **19** (12.0 g) as a brown oil which was used without further purification.

35 Step 3.

[0126] To a solution of $\text{NH}_3 \cdot \text{H}_2\text{O}$ (200 mL) in dioxane (100 mL) was added **19** (11.0 g, 33.6 mmol) in dioxane (100 mL) at 0°C. After 30 minutes at 15°C, the reaction mixture was diluted with water (100 mL) and then extracted with ethyl acetate (3 \times 300 mL). The combined organic phase was washed with saturated brine (2 \times 300 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated *in vacuo* to give a residue which was purified by re-crystallization from methyl-t-butylether (100 mL) to give **20** (1.0 g) as a white solid. **LCMS** (ESI): m/z 276.0 (M-H).

40 Step 4.

[0127] To a solution of **20** (200 mg, 0.72 mmol) in THF (10.0 mL) was added NaBH_4 (274 mg, 7.24 mmol) portion wise at 0°C. After addition, $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (1.03 g, 7.24 mmol) was added portion wise. The resulting mixture was stirred at 70°C for 14 hours. The reaction mixture was quenched with water (40 mL) and then extracted with ethyl acetate (3 \times 50 mL). The organic phase was washed with saturated brine (2 \times 50 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated *in vacuo* to give **21** (160 mg, crude) as a white solid which was used without further purification. **LCMS** (ESI): m/z 262.0 (M-H).

50 Step 5.

[0128] To a solution of **21** (120 mg, crude) in DMF (6.0 mL) was added Cs_2CO_3 (298 mg, 0.92 mmol) and BnBr (117 mg, 0.69 mmol). The mixture was stirred at 30°C for 14 hours. The reaction mixture was filtered and then diluted with water (20 mL) and extracted with ethyl acetate (3 \times 20 mL). The organic layer was washed with water (3 \times 15 mL) and saturated brine (2 \times 20 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to give **22** (200 mg) as a yellow oil, which was used directly into the next step without further purification.

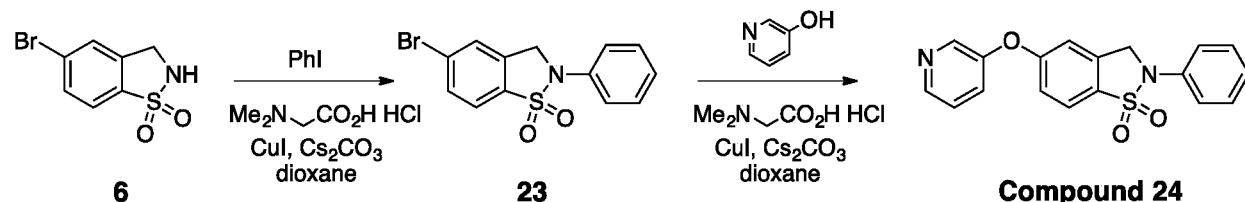
Step 6.

[0129] A mixture of **22** (140 mg), pyridine-3-ol (45 mg, 0.48 mmol), Cul (30 mg, 0.16 mmol), N,N-dimethylglycine hydrochloride (11 mg, 0.079 mmol) and Cs_2CO_3 (259 mg, 0.79 mmol) in dioxane (6.0 mL) was degassed and purged with N_2 (3X). The mixture was stirred at 100°C for 14 hours and then filtered. The filtrate was concentrated under reduced pressure to give a residue, which was purified by prep-HPLC to afford **Compound 23** (72 mg, 91%) as a colorless oil. **1H NMR** (MeOD , 400MHz) δ 8.79-8.78 (d, 1H), 8.68-8.67 (d, 1H), 8.33-8.31 (m, 1H), 8.11-8.09 (m, 1H), 7.46-7.44 (m, 2H), 7.39-7.32 (m, 3H), 7.26-7.25 (d, 1H), 7.15-7.14 (d, 1H), 4.44 (s, 2H), 4.24 (s, 2H), 2.63 (s, 3H); **LCMS** (ESI): m/z 486.2 (M+H).

Example 24

Synthesis of Compound 24

[0130]



Step 1.

[0131] To a solution of **6** (1.00 g, 3.63 mmol) and iodobenzene (889 mg, 4.36 mmol) in dioxane (15.0 mL) was added Cul (276 mg, 1.45 mmol), 2-(dimethylamino)acetic acid hydrochloride (101 mg, 7.26 mmol), and cesium carbonate (2.36 g, 7.26 mmol). The resulting mixture was heated to 90°C and allowed to stir under inert atmosphere for 12 h. Upon completion, the reaction mixture was filtered, concentrated under reduced pressure, and the resulting oil was triturated with methyl-*t*-butyl ether (10 mL) to afford **23** (700 mg). LCMS (ESI): m/z 324.0 (M+H).

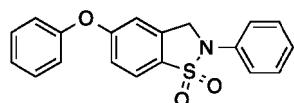
Step 2.

[0132] To a solution of **23** (350 mg, 1.08 mmol) and pyridin-3-ol (123 mg, 1.30 mmol) stirred in dioxane (4.0 mL) was added Cul (82 mg, 0.43 mmol), cesium carbonate (703 mg, 2.16 mmol) and 2-(dimethylamino)acetic acid hydrochloride (30 mg, 0.22 mmol). The reaction mixture was stirred at 90°C under N_2 for 12 h. Upon completion, the reaction mixture was filtered and concentrated under reduced pressure. Purification by HPLC (0.04%HCl/CH₃CN/H₂O system) resulted in **Compound 24** (50 mg, 26%). **1H NMR** (DMSO-*d*₆, 400MHz) δ 8.59-8.58 (d, 2H), 8.54-8.53 (d, 1H), 8.04-8.02 (m, 1H), 7.47-7.45 (m, 1H), 7.42-7.41 (m, 4H), 7.33-7.31 (m, 1H), 7.28-7.20 (m, 1H), 5.0 (s, 2H); **LCMS** (ESI): m/z 339.0 (M+H).

Example 25

Synthesis of Compound 25

[0133]

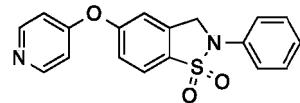


[0134] **Compound 25** was prepared in a manner similar to **Compound 24**. **1H NMR**: (DMSO-*d*₆, 400MHz) δ 8.00-7.98 (d, 1H), 7.50-7.40 (m, 6H), 7.21-7.17 (m, 6H), 4.99 (s, 2H); **LCMS** (ESI): m/z 338.0 (M+H).

Example 26

Synthesis of Compound 26

5 [0135]



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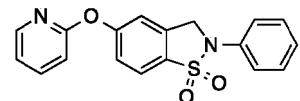
[0136] Compound 26 was prepared in a manner similar to Compound 24. **¹H NMR** (DMSO, 400MHz) δ 8.17-8.15 (d, 1H), 7.81 (s, 1H), 7.74-7.72 (d, 2H), 7.58-7.55 (t, 1H), 7.49-7.48 (m, 4H), 7.24-7.23 (m, 1H), 6.55-6.53 (d, 1H), 6.41-6.38 (t, 1H), 5.11 (s, 2H); **LCMS** (ESI): m/z 339.0 (M+H).

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Example 27

Synthesis of Compound 27

20 [0137]



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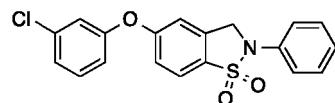
[0138] Compound 27 was prepared in a manner similar to Compound 24. **¹H NMR** (DMSO-*d*₆, 400MHz) δ 8.16-8.14 (d, 1H), 7.74-7.72 (d, 1H), 7.56-7.55 (d, 1H), 7.49-7.48 (m, 3H), 6.55-6.53 (d, 1H), 6.41-6.39 (m, 1H), 5.11 (s, 2H); **LCMS** (ESI): m/z 339.0 (M+H).

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Example 28

Synthesis of Compound 28

35 [0139]



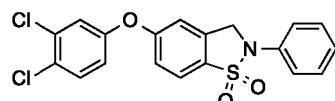
40

[0140] Compound 28 was prepared in a manner similar to Compound 24. **¹H NMR** (DMSO-*d*₆, 400MHz) δ 8.03-8.01 (d, 1H), 7.51-7.41 (m, 8H), 7.34-7.18 (m, 3H), 5.01 (s, 2H); **LCMS** (ESI): m/z 372.0 (M+H).

45 **Example 29**

Synthesis of Compound 29

50 [0141]



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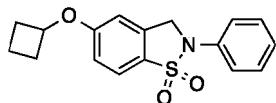
[0142] Compound 29 was prepared in a manner similar to Compound 24. **¹H NMR** (DMSO-*d*₆, 400MHz) δ 8.03-8.01 (d, 1H), 7.75-7.72 (d, 1H), 7.58 (s, 1H), 7.48-7.29 (m, 4H), 7.23-7.20 (m, 4H), 5.00 (s, 2H); **LCMS** (ESI): m/z 405.9 (M+H).

Example 30

Synthesis of Compound 30

5 [0143]

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[0144] Compound 30 was prepared in a manner similar to Compound 24. **¹H NMR** (DMSO-*d*₆ 400MHz) δ 7.88-7.86 (d, 1H), 7.48-7.41 (m, 4H), 7.20-7.16 (m, 1H), 7.20-7.16 (m, 2H), 4.96-4.87 (d, 2H), 4.83-4.80 (m, 1H), 2.41-2.11 (m, 2H), 2.09-2.04 (m, 2H), 1.83-1.81 (m, 1H), 1.71-1.64 (m, 1H); **LCMS** (ESI): m/z 316.0 (M+H).

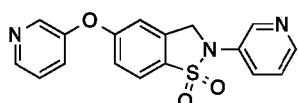
15

Example 31

Synthesis of Compound 31

20 [0145]

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[0146] Compound 31 was prepared in a manner similar to Compound 24. **¹H NMR** (DMSO-*d*₆, 400MHz) δ 8.71-8.69 (d, 2H), 8.61-8.60 (d, 2H), 8.15-8.13 (d, 2H), 7.90-7.88 (m, 1H), 7.72-7.37 (m, 2H), 5.17 (s, 2H); **LCMS** (ESI): m/z 340.0 (M+H).

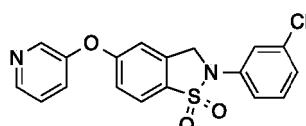
30

Example 32

Synthesis of Compound 32

35 [0147]

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[0148] Compound 32 was prepared in a manner similar to Compound 24. **¹H NMR** (DMSO-*d*₆ 400MHz) δ 8.57-8.54 (d, 2H), 8.07-8.05 (d, 1H), 7.72-7.59 (d, 1H), 7.48-7.42 (d, 1H), 7.40-7.38 (m, 1H), 7.33-7.26 (m, 2H), 5.05 (s, 2H); **LCMS** (ESI): m/z 373.0 (M+H).

45

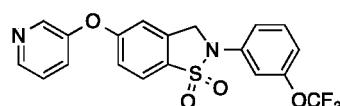
Example 33

Synthesis of Compound 33

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[0149]

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[0150] Compound 33 was prepared in a manner similar to Compound 24. **¹H NMR** (DMSO-*d*₆ 400MHz) δ 8.57-8.53

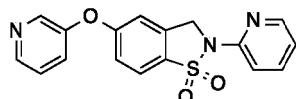
(d, 1H), 8.08-8.06 (d, 1H), 7.60-7.58 (m, 1H), 7.45-7.26 (m, 2H), 5.07 (s, 2H); **LCMS** (ESI): m/z 423.0 (M+H).

Example 34

5 Synthesis of Compound 34

[0151]

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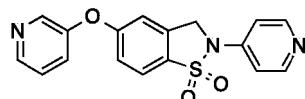
15 [0152] Compound 34 was prepared in a manner similar to Compound 24. **1H NMR** (DMSO-*d*₆, 400MHz) δ 8.58-8.48 (m, 2H), 8.42 (d, 1H), 8.06 (d, 1H), 7.93-7.86 (m, 1H), 7.70 (dd, 1H), 7.55 (dd, 1H), 7.37-7.29 (m, 3H), 7.17 (dd, 1H), 5.12 (s, 2H); **LCMS** (ESI): m/z 340.0 (M+H).

Example 35

20 Synthesis of Compound 35

[0153]

25



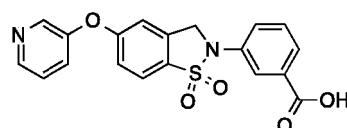
30 [0154] Compound 35 was prepared in a manner similar to Compound 24. **1H NMR** (DMSO-*d*₆, 400MHz) δ 8.82 (s, 1H), 8.72-8.70 (d, 3H), 8.22-8.14 (d, 1H), 8.01-8.00 (d, 1H), 7.99-7.86 (m, 1H), 7.86-7.83 (d, 2H), 5.28 (s, 2H); **LCMS** (ESI): m/z 340.0 (M+H).

Example 36

35 Synthesis of Compound 36

[0155]

40



45 [0156] Compound 36 was prepared in a manner similar to Compound 24. **1H NMR** (CD₃OD 400MHz) δ 8.81 (s, 1H), 8.68-8.67 (d, 1H), 8.28-8.11 (d, 1H), 8.06-8.00 (m, 2H), 7.88-7.86 (d, 1H), 7.56-7.48 (d, 1H), 5.03 (s, 2H); **LCMS** (ESI): m/z 383.0 (M+H).

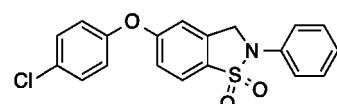
Example 37

50

Synthesis of Compound 37

[0157]

55



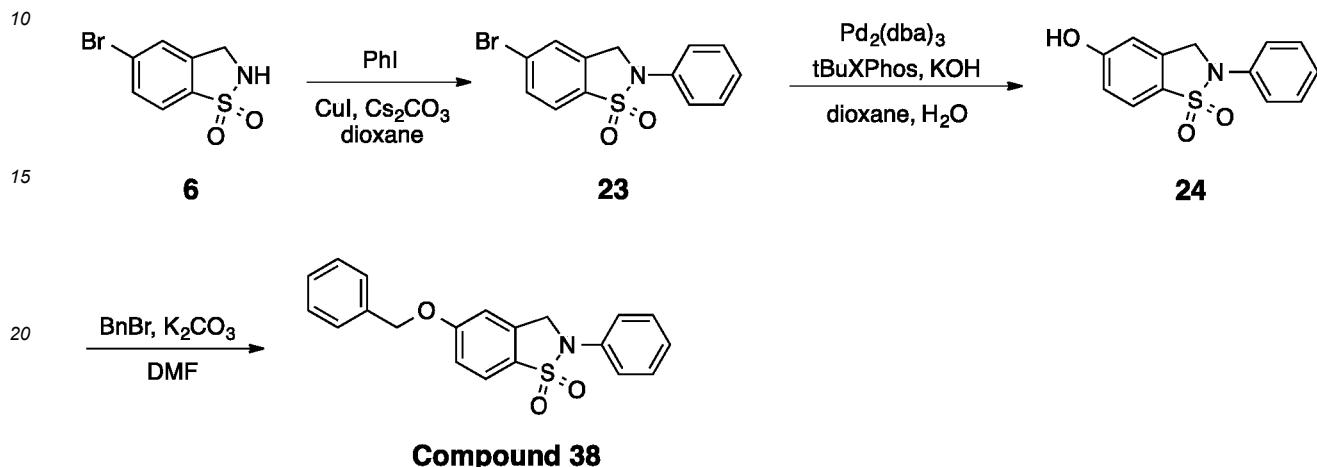
[0158] Compound 37 was prepared in a manner similar to Compound 24. ^1H NMR (CD_3OD , 400MHz) δ 7.85-7.83 (d, 1H), 7.48-7.40 (m, 5H), 7.20-7.17 (m, 4H), 7.15-6.85 (m, 1H), 4.560 (s, 2H); LCMS (ESI): m/z 372.0 (M+H).

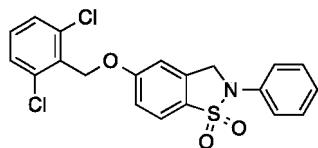
Example 38

5

Synthesis of Compound 38

[0159]



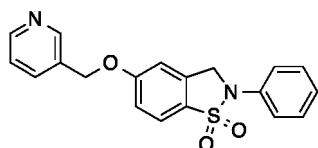


[0164] Compound 39 was prepared in a manner similar to Compound 38. **1H NMR** ($\text{DMSO}-d_6$, 400MHz) δ 7.95-7.93 (d, 1H), 7.61-7.59 (d, 2H), 7.59-7.51 (m, 6H), 7.49-7.45 (d, 1H), 7.35-7.19 (m, 1H), 5.38 (s, 2H), 5.03 (s, 2H); **LCMS** (ESI): m/z 420.0 (M+H).

Example 40

Synthesis of Compound 40

〔0165〕

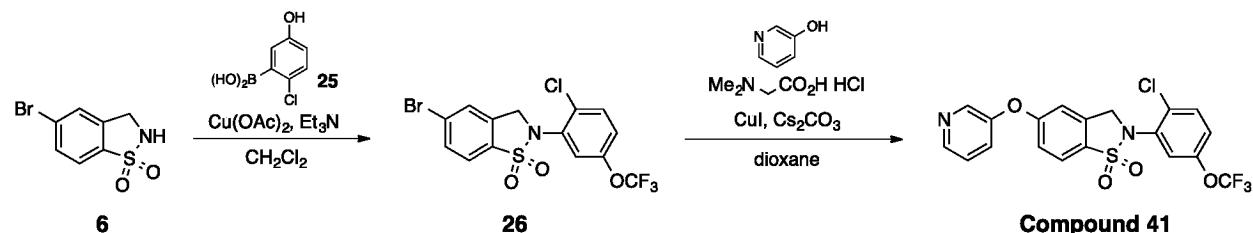


[0166] Compound **40** was prepared in a manner similar to **Compound 38**. **1H NMR** ($\text{DMSO}-d_6$, 400MHz) δ 8.24-8.22 (d, 1H), 7.96-7.94 (d, 1H), 7.74 (s, 1H), 7.48-7.45 (m, 4H), 7.34-7.22 (m, 3H), 7.19-7.17 (m, 1H), 5.39 (s, 2H), 5.01 (s, 2H); **LCMS** (ESI): m/z 353.0 (M+H).

Example 41

Synthesis of Compound 41

[0167]



Step 1.

[0168] A mixture of **6** (120 mg, 0.48 mmol), **25** (140 mg, 0.58 mmol), Cu(OAc)₂ (88 mg, 0.48 mmol), Et₃N (98 mg, 0.97 mmol) and 4A molecular sieves (250 mg) in CH₂Cl₂ (10.0 mL) was degassed and purged with O₂ (3X). After stirring for 1 h at 15°C for 1 hour, the reaction mixture was filtered, diluted with water (20 mL), and extracted with CH₂Cl₂ (3 × 20 mL). The organic layer was washed with brine (2 × 20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give **26** (220 mg) as a yellow solid which was used directly in the next step without further purification.

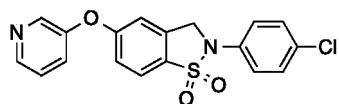
[0169] A mixture of **26** (220 mg, crude material), pyridine-3-ol (48 mg, 0.51 mmol), Cul (32 mg, 0.17 mmol), N,N-dimethylglycine hydrochloride (12 mg, 0.084 mmol) and Cs₂CO₃ (275 mg, 0.084 mmol) in dioxane (3.0 mL) was degassed and purged with N₂ (3X). The mixture was stirred at 100°C for 12 hours and then filtered. The filtrate was concentrated under reduced pressure to give a residue, which was purified by prep-HPLC to afford **Compound 41** (2.6 mg, 1%) as a white solid. **1H NMR** (CD₃OD, 400MHz) δ 8.80 (s, 1H), 8.66 (s, 1H), 8.26-8.24 (d, 1H), 8.02-7.99 (d, 2H), 7.74-7.72 (d, 1H), 7.67 (s, 1H), 7.49-7.44 (m, 3H), 4.95 (s, 2H); **LCMS** (ESI): m/z 457.0 (M+H).

Example 42

Synthesis of Compound 42

5 [0170]

10



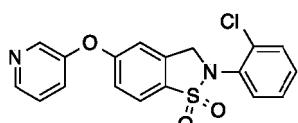
[0171] Compound 42 was prepared in a manner similar to Compound 41. **1H NMR** (400 MHz, CD₃OD) δ 8.37 (d, *J*=8.53 Hz, 1H), 8.16 (s, 1H), 8.03 (d, *J*=9.04 Hz, 1H), 7.56-7.38 (m, 7H), 4.99 (s, 2H); **LCMS** (ESI): m/z 457.0 (M+H).

15 Example 43

Synthesis of Compound 43

20 [0172]

25



[0173] Compound 43 was prepared in a manner similar to Compound 41. **1H NMR** (400 MHz, CD₃OD) δ 7.93 (d, *J*=8.38 Hz, 1H), 7.86 (d, *J*=7.94 Hz, 2H), 7.73-7.57 (m, 2H), 7.50-7.32 (m, 3H), 7.29 (s, 1H), 4.88 (s, 2H); **LCMS** (ESI): m/z 457.0 (M+H).

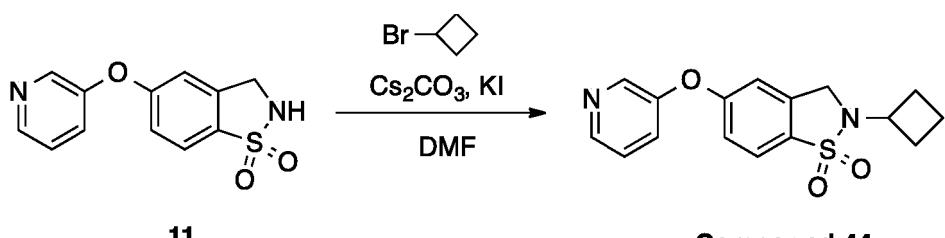
30

Example 44

Synthesis of Compound 44

35 [0174]

40



45

Compound 44

50

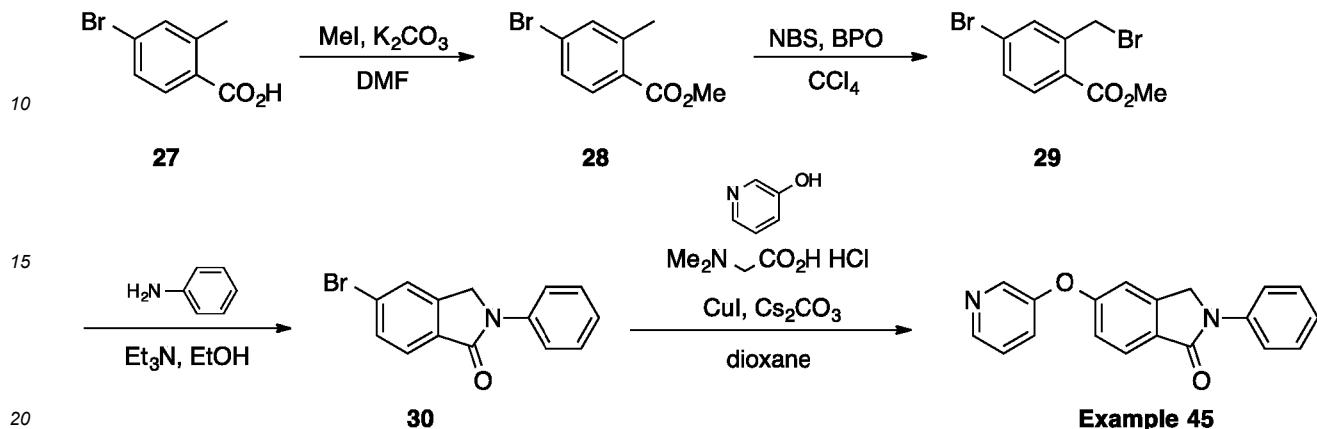
[0175] A mixture of **11** (40 mg, 0.15 mmol), bromocyclobutane (103 mg, 0.76 mmol), KI (25 mg, 0.15 mmol), Cs₂CO₃ (99 mg, 0.31 mmol) in DMF (2.0 mL) was degassed and purged with N₂ (3X). The reaction mixture was stirred at 50°C for 12 hours under N₂ atmosphere and then quenched with H₂O (10 mL). The solution was extracted with ethyl acetate (2 × 10 mL) and the combined organic layer was washed with brine (2 × 10 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. Purification by prep-HPLC provided **Compound 44** (33 mg, 59%) as a slight yellow solid. **1H NMR** (DMSO-*d*₆, 400MHz) δ 8.61 (d, 1H), 8.55 (d, 1H), 7.89 (d, 1H), 7.80 (d, 1H), 7.64 (dd, 1H), 7.31-7.22 (m, 2H), 4.43 (s, 2H), 4.05 (m, 1H), 2.37-2.24 (m, 2H), 2.22-2.11 (m, 2H), 1.78 (m, 2H); **LCMS** (ESI): m/z 317.1 (M+H).

55

Example 45

Synthesis of Compound 45

5 [0176]



Step 1.

25 [0177] To **27** (3.0 g, 14.0 mmol) and CH_3I (3.96 g, 27.9 mmol) in DMF (30 mL) was added K_2CO_3 (2.89 g, 20.9 mmol). The reaction mixture was stirred at 25°C for 12 h and then quenched with H_2O (20 mL). The solution was extracted with ethyl acetate (3 × 100 mL) and the organic layer was washed with H_2O (3 × 100 mL) and concentrated to afford **28** (2.9 g, 82%).

Step 2.

30 [0178] To a solution of **28** (1.0 g, 4.37 mmol) and NBS (0.93 g, 5.24 mmol) in CCl_4 (10 mL) was added BPO (106 mg, 0.4400 mmol). The reaction mixture was stirred at 80°C for 5 h. Upon completion, the reaction was quenched with H_2O (10 mL) and extracted with ethyl acetate (3 × 20 mL). The the organic layer was washed with H_2O (3 × 10 mL), concentrated, and purified by prep-TLC (petroleum : ethyl acetate = 20:1) to afford **29** (610 mg, 41%).

Step 3.

35 [0179] To a solution of **29** (500 mg, 1.62 mmol) and aniline (166 mg, 1.78 mmol) in EtOH (2 mL) was added diisopropylethylamine (230 mg, 1.78 mmol). The reaction mixture was stirred at 90°C for 12 h, cooled to 0°C, and then filtered. The crude material was washed with EtOH to afford **30** (400 mg, 77%) as a white solid without further purification.

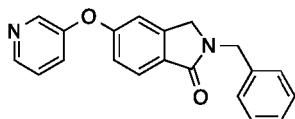
Step 4.

40 [0180] To a solution of **30** (120 mg, 0.42 mmol) and pyridin-3-ol (59 mg, 0.62 mmol) in dioxane (2 mL) was added Cs_2CO_3 (407 mg, 1.25 mmol), CuI (32 mg, 0.17 mmol) and 2-(dimethylamino)acetic acid hydrochloride (23 mg, 0.17 mmol). The reaction mixture was stirred at 110°C under N_2 for 12 h and then filtered and concentrated. Purification by prep-HPLC afforded **Compound 45** (100 mg, 72%). $^1\text{H NMR}$ ($\text{DMSO}-d_6$, 400MHz) δ 8.71 (s, 1H), 8.71-8.62 (d, 1H), 7.98-7.96 (d, 1H), 7.88-7.84 (m, 4H), 7.46-7.40 (m, 3H), 7.31-7.29 (m, 1H), 7.18 (m, 1H), 5.00 (s, 2H); **LCMS** (ESI): m/z 303.1 ($\text{M}+\text{H}$).

50 **Example 46**

Synthesis of Compound 46

55 [0181]



5

[0182] Compound 46 was prepared in a manner similar to Compound 45. **¹H NMR** (DMSO-*d*₆, 400MHz) δ 8.83-8.59 (m, 2H). 7.99 (d, 1H), 7.87-7.76 (m, 2H), 7.38-7.32 (m, 3H), 7.31-7.25 (m, 4H), 4.72 (s, 2H), 4.35 (s, 2H); **LCMS** (ESI): m/z 317.1 (M+H).

10 BIOLOGICAL EXAMPLES

Example 47

Human GPR120 β-Arrestin Recruitment Assay

15

[0183] This in vitro assay tests compounds' ability to activate intracellular signaling via β-Arrestin recruitment to heterologously expressed human GPR120. This functional cellular assay utilizes enzyme fragment complementation with β-galactosidase (β-gal) as a functional reporter (DiscoverRx PathHunter® β-Arrestin assay platform). The human GPR120 receptor (GenBank accession Number NM_181745) was fused in frame with the small enzyme fragment ProLink™ and co-expressed in CHO-K1 cells with a fusion protein of P-Arrestin 2 and the larger, N-terminal deletion mutant of β-gal. Activation by a GPR120 agonist stimulates binding of β-arrestin to the ProLink-tagged GPCR and forces complementation of the two enzyme fragments, resulting in the formation of an active β-gal enzyme. This interaction leads to an increase in enzyme activity that can be measured using chemiluminescent PathHunter® Detection Reagents.

20

[0184] One day prior to the assay, cells were seeded in a total volume of 20μl of growth medium into white walled 384-well microplates and incubated at 37°C / 5% CO₂ overnight. On the day of the assay, growth medium was removed and 20μl assay buffer (HBSS + 10mM HEPES + 0.1% heat-inactivated BSA) were added to each well.

25

[0185] Test compounds were dissolved in 100% DMSO to a concentration of 10 mM to provide stock solutions. Serial dilutions were performed from stock solutions into assay buffer to obtain intermediate concentrations of 5-fold higher than the concentrations to be tested. 5μl of the 5x compound solutions were added to the cells and the assay plates were incubated at 37°C for 90 minutes. The final concentration of compounds tested in the assay ranged from 1.5nM to 100μM. Following incubation, 12.5μl of PathHunter® detection reagent were added to each well, and plates were incubated at room temperature for 60 minutes. Chemiluminescence was read using an EnVision plate reader (PerkinElmer), raw data were expressed as relative light units (RLU).

30

[0186] To determine agonist potencies (EC₅₀ values), non-linear least-squares curve fits of the raw data (RLU) were performed in the GraphPad Prism software package, using the 4-parameter model with variable Hill Slope:

35

$$Y = Bottom + \frac{Top - Bottom}{1 + 10^{((logEC50 - x) * Hill\ Slope)}}$$

40

[0187] Reported below in **Table 1** are pEC₅₀ values (pEC₅₀ = -log(EC₅₀) from curve fit) for compounds of Formula I in this assay, β-Arr pEC50.

45

Example 48

Human GPR120 Calcium-Release Assay

46

[0188] This in vitro assay tests compounds' ability to activate heterologously expressed human GPR120 via G-protein coupling leading to generation of inositol 1,4,5-triphosphate and mobilization of intracellular calcium. This functional cellular assay is based on the luminescence of mitochondrial aequorin following intracellular Ca²⁺ release. Aequorin is a photoprotein isolated from the *jellyfish Aequorea victoria*. The active protein is formed in the presence of molecular oxygen from apoaequorin and its cofactor coelenterazine. Binding of Ca²⁺ to the active protein induces a conformational change, resulting in oxidation of coelenterazine and subsequent blue luminescence.

47

[0189] The short variant of the human GPR120 receptor (GenBank accession Number AAI01176) was stably expressed in a CHO-K1 cell line coexpressing Gα16 and mitochondrial apoaequorin.

48

[0190] Cells were grown to mid-log phase in culture media without antibiotics, were detached with PBS/EDTA, centrifuged and resuspended in assay buffer (DMEM-F12 medium with 15mM HEPES pH 7.0 and 0.1% protease free BSA) at a concentration of 10⁶ cells/mL. Cells were incubated at room temperature for at least 4 hours with 5μM coelenterazine

h.

[0191] Test compounds were dissolved in 100% DMSO to a concentration of 20 mM to provide stock solutions. Serial dilutions were performed from stock solutions in 100% DMSO to obtain intermediate concentrations 200-fold higher than the concentrations to be tested. Each sample was diluted 100-fold into assay buffer. 50 μ l of these compound solutions were dispensed into each well of 96-well assay plates. The final concentration of compounds tested in the assay ranged from 5nM to 100 μ M. α -Linolenic acid was used as a reference compound. Each test was performed in duplicate.

[0192] To start the assay, 50 μ l of cell suspension were added to each well of the assay plate. The resulting luminescence was recorded using a Hamamatsu Functional Drug Screening System 6000 (FDSS 6000), and raw data were expressed as relative light units (RLU).

[0193] To determine agonist potencies (EC₅₀ values), non-linear least-squares curve fits of the raw data (RLU) were performed in the GraphPad Prism software package, using the 4-parameter model with variable Hill Slope:

$$Y = Bottom + \frac{Top - Bottom}{1 + 10^{((logEC50 - x) * Hill\ Slope)}}$$

[0194] Reported below in **Table 1** are pEC₅₀ values (pEC₅₀ = -log(EC₅₀) from curve fit) for representative compounds of Formula I in this assay, Ca2+ pEC50.

Table 1. Activity of compounds of Formula I in in vitro assays.

| Compound # | β -Arr pEC50 | Ca2+ pEC50 |
|------------|--------------------|------------|
| 1 | 5.7 | 6.2 |
| 2 | 6.3 | 6 |
| 3 | 6.8 | 5.4 |
| 4 | 6.6 | 5.1 |
| 5 | 5.8 | |
| 6 | < 5.0 | |
| 7 | 5.4 | 5.7 |
| 8 | 5.2 | |
| 9 | 5.9 | 5.8 |
| 10 | 5.5 | 5.6 |
| 11 | 5.1 | 5.4 |
| 12 | < 4.5 | |
| 13 | < 5.0 | |
| 14 | 4.9 | 4.7 |
| 15 | 6.3 | 6.1 |
| 16 | 5.5 | |
| 17 | < 5.0 | |
| 18 | < 5.0 | |
| 19 | 5.1 | 4.8 |
| 20 | 5.5 | 5 |
| 21 | < 4.5 | |
| 22 | < 4.5 | |
| 23 | 5.7 | |
| 24 | 5.1 | 5.6 |
| 25 | 6 | 5.9 |

(continued)

| Compound # | β -Arr pEC50 | Ca2+ pEC50 |
|------------|--------------------|------------|
| 26 | < 4.5 | |
| 27 | < 4.5 | |
| 28 | 6.1 | 4.4 |
| 29 | < 4.5 | < 4.0 |
| 30 | 5.6 | < 4.0 |
| 31 | < 5.0 | |
| 32 | 5.8 | |
| 33 | 5.3 | |
| 34 | 4.8 | 5 |
| 35 | 4.9 | |
| 36 | < 5.0 | |
| 37 | < 5.0 | |
| 38 | 5.3 | |
| 39 | 5 | |
| 40 | < 4.5 | |
| 41 | < 4.5 | |
| 42 | 5.4 | |
| 43 | < 5.0 | |
| 44 | 4.9 | |
| 45 | < 5.0 | |
| 46 | 5.2 | 5 |

[0195] The results above show that the compounds of the invention, as illustrated in the examples above and generally as defined by Formula 1, are potent GPR120 agonists that will find application in the treatment of T2D. While, as disclosed in the detailed description above, these compounds can be administered via any route of administration and at various frequencies, in one preferred embodiment, they are administered once a day to T2D patients for treatment and control of that condition in the form of a tablet or capsule, taken orally.

Example 49

Biological Example: GPR120 C57BL/6J Mouse Oral Glucose Tolerance Test

[0196] An oral glucose tolerance test (OGTT) was performed with certain compounds to determine their acute effect on glucose excursions.

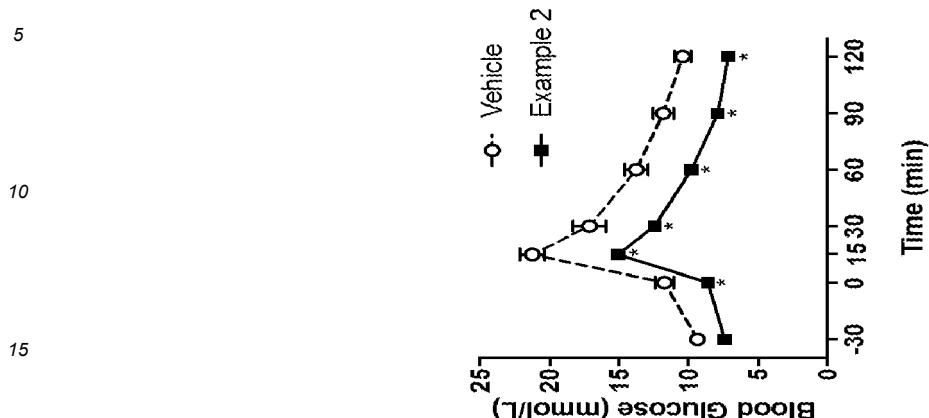
[0197] Male C57BL/6J mice aged 8-10 weeks and kept on a regular chow diet were used for the study. 10 Mice were used per treatment group, with individual mice weighing in the range of 24-30 grams on study day, and a mean weight of 27.2 - 27.3 grams for each treatment group.

[0198] Test articles were prepared as suspensions in dosing vehicle (0.5% hydroxypropyl methylcellulose and 2% Tween-20 in water) at a concentration of 10 mg/mL by mixing and sonication.

[0199] The mice were fasted for 6 hours prior to dosing of vehicle or test articles at 100 mg/kg (10 mL/kg) by oral gavage. Glucose was dosed (PO) at 3g/kg 30 min after dosing of test articles. Animals were bled via tail snip to determine basal glucose levels 30 min prior to the glucose challenge, and again at 0, 15, 30, 60, 90 and 120 minutes following the glucose challenge. A Johnson & Johnson OneTouch Glucometer was used to determine glucose levels in all blood samples.

[0200] Glucose values were entered into an Excel sheet, and mean values \pm standard error of the mean were graphed

in GraphPad Prism. Significance of difference between groups was analyzed by performing two-way RM ANOVA for the time course study. P values less than 0.05 were considered statistically significant.



Example 50

Anti-Inflammatory Activity In LPS-Stimulated Human Peripheral Blood Mononuclear Cells

[0201] The ability of compounds of this invention to inhibit TNF α production was assessed by using human peripheral blood mononuclear cells (hPBMC) which synthesize and secrete TNF α when stimulated with lipopolysaccharide (LPS).

[0202] Mononuclear Cell packs collected by and purchased from Key Biologics were used for the preparation of hPBMC. Briefly, cell product was steriley removed from the phoresis bag, carefully layered onto pre-warmed Ficoll (Histopaque 1077) and centrifuged at 1,800 x g for 15 minutes at room temperature with the brake off. Following centrifugation, the interface was removed and added to sterile Dulbecco's Phosphate Buffered Saline (DPBS). The cells were then pelleted at 300 x g for ten minutes at room temperature. The cells were resuspended in fresh DPBS then repelleted to minimize platelet contamination. The subsequent pellet was resuspended in DPBS and the cells counted. Cells were repelleted and then cryopreserved at 1×10^8 cells per ml in DMEM / 30% FBS / 10% DMSO. For all hPBMC preparations, individual donors were kept separate throughout the entire process. For the assay, hPBMC were seeded into flat-bottom 96-well plates at 500,000 cells/well in 80 μ l assay medium (DMEM, 0.1% FBS, 1% penicillin / streptomycin) and allowed to recover in a 37°C incubator for one hour before the addition of compounds.

[0203] Compounds were solubilized from powder as 20mM stocks with 100% DMSO and then serially diluted into assay medium to prepare 10x stocks to achieve five concentrations (100 μ M, 30 μ M, 10 μ M, 3 μ M and 1 μ M) in the assay. All compound dilutions were added to the plates containing hPBMC (10 μ l in final assay volume of 100 μ l) and incubated at 37°C for an hour before the addition of stimulus. Control wells received 10 μ l vehicle (media containing 5% DMSO).

[0204] For the LPS challenge, a 1mg/ml stock solution of lipopolysaccharide (LPS) was diluted 1000-fold into assay medium (10 μ l LPS + 10ml media). All wells except the "Unstimulated" control wells received 10 μ l of LPS. The "Unstimulated" control wells received 10 μ l media. The plates were incubated for 4 hours at 37°C. After 4 hours, the plates were centrifuged at 1,200 rpm for 5 minutes and culture media supernatants were collected into fresh 96-well plates.

[0205] TNF α levels in culture supernatants were determined by immunoassay using the Meso Scale Diagnostics electrochemiluminescent immunoassay system. Meso Scale V-plex 96-well plates (Meso Scale Diagnostics, Rockville, MD) were used for detection of TNF α as directed by the manufacturer (overnight incubation protocol). Samples were diluted 100-fold. TNF α concentrations were determined by interpolating against a standard curve and then multiplying by 100 to arrive at "pg/ml" values. TNF α release was reported as % of vehicle treated LPS stimulated cells.

5

10

15

20 REFERENCES

[0207]

25 1. Data for diabetes: World Health Organization, Fact Sheet No. 312 (<http://www.who.int/mediacentre/factsheets/fs312/en/>)

2. Hirasawa et al. Nat. Med. 2005, 11:90-94.

3. Oh et al. Cell 2010, 142:687-698.

4. Ichimura et al. Nature 2012, 483:350-354.

5. Cornall et al. Drug Disc. Today 2014, 19:670-679.

30 5a. Nobili et al. PLOSone 2014, 9: e88005.

6a. Wellhauser et al. J Neuroinflamm 2014, 11: 60.

7a. Dragano et al. J Neuroinflamm 2017, 17:91.

8a. Heneka et al. Nature 2013, 493: 674.

9a. Yan et al. Immunity 2013, 38: 1154.

35 10a. Tan et al. Cell Death Dis 2014, 5: e1382.

11a. Kaushal et al. Cell Death Differentiation 2015, 22: 1676.

6. Suzuki et al. J. Med. Chem. 2008, 51:7640-7644.

7. Hara et al. Naunyn Schmied. Arch. Pharmacol. 2009, 380:247-255.

40 8. Shimpukade et al. J. Med. Chem. 2012, 55:4511-4515.

9. Hudson et al. Mol Pharmacol. 2013, 84:710-725.

10. Oh et al. Nat. Med. 2014, 20:942-947.

11. Sparks et al. Bioorg. Med. Chem. Lett. 2014, 24:3100-3103.

12. Tanaka et al. Naunyn-Schmiedeberg's Arch Pharmacol. 2008, 377:523-527.

45 13. Lu et al. Am. J. Gastrointest. Liver Physiol. 2012, 303:G367-G376.

14. Suckow et al. J. Bio. Chem. 2014, 289: 15751-15763.

15. US 20080167378

16. WO 2008066131

17. WO 2008103501

50 18. WO 2008139987

19. WO 2009147990

20. US 20100130559

21. WO 2010048207

22. WO 2010080537

23. WO 2011159297

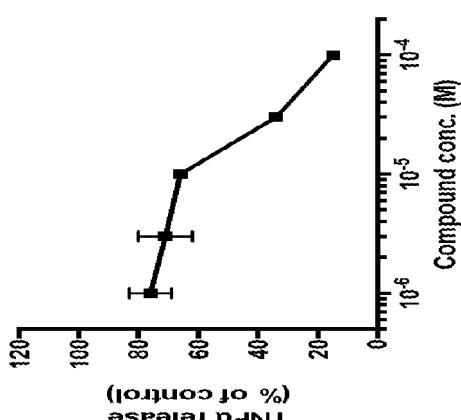
55 24. US 20110313003

25. WO2013139341

26. WO 2014069963

27. US 20140275172

Example 2

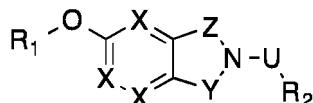


28. US 20140275179
 29. WO 20140275182
 30. WO 2014059232
 31. WO 2014159794
 5 32. US 20140275173
 33. WO 2010104195

Claims

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1. A compound of formula:

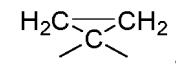


wherein

20

each X independently is CH, CR₃, or N;
 Y is SO₂;
 Z is -CH₂-, -CH(CH₃)-, -C(CH₃)₂-,

25



-(CO)CH₂-, or -CHCH-;

U is CH₂, -CH(CH₃)-, -C(CH₃)₂-, or -CH₂CH₂-;

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R₁ is an optionally substituted alkyl group, an optionally substituted 3-7 membered cycloalkyl or heterocyclyl group, an optionally substituted 6-membered aryl group, an optionally substituted 5- or 6-membered heteroaryl group, an optionally substituted 5,6- or 6,6-membered bicyclic heteroaryl group, or an optionally substituted bicyclic aryl group;

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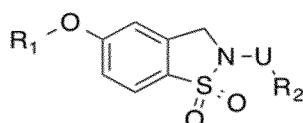
R₂ is an optionally substituted 3-7 membered cycloalkyl or heterocyclyl group, an optionally substituted 6-membered aryl group, an optionally substituted 5- or 6-membered heteroaryl group, an optionally substituted 5,6- or 6,6-membered bicyclic aryl or heteroaryl group, or an optionally substituted bicyclic aryl group; and

R₃ is a halogen, or an optionally substituted alkyl or alkoxy group.

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2. The compound of claim 1 of formula

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wherein

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U is CH₂, -CH(CH₃)-, -C(CH₃)₂-, or -CH₂CH₂-;

R₁ is an optionally substituted alkyl group, an optionally substituted 3-7 membered cycloalkyl or heterocyclyl group, an optionally substituted 6-membered aryl group, an optionally substituted 5- or 6-membered heteroaryl group, an optionally substituted 5,6- or 6,6-membered bicyclic heteroaryl group, or an optionally substituted bicyclic aryl group; and

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R₂ is an optionally substituted 3-7 membered cycloalkyl or heterocyclyl group, an optionally substituted 6-membered aryl group, an optionally substituted 5- or 6-membered heteroaryl group, an optionally substituted 5,6- or 6,6-membered bicyclic heteroaryl group, or an optionally substituted bicyclic aryl group.

3. A compound of the structure



or a tautomer thereof, or an isotopomer thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt of each thereof, or a pharmaceutically acceptable solvate of each of the foregoing.

55 4. A pharmaceutical composition comprising a compound of any one of claims 1-3 and a pharmaceutically acceptable excipient.

5. The compound of any one of claims 1-3 or the composition of claim 4 for use in a method for agonizing GPR120, wherein said method comprises contacting the GPR120 with said compound or said composition.

5 6. The compound of any one of claims 1-3 or the composition of claim 4 for use in a method for modulating metabolism in a mammal, wherein said method comprises contacting GPR120 in the mammal with an amount of said compound or said composition.

10 7. The compound of any one of claims 1-3 or the composition of claim 4 for use in a method for reducing inflammation in a mammal, wherein said method comprises contacting GPR120 in the mammal with an amount of said compound or said composition.

15 8. The compound of any one of claims 1-3 or the composition of claim 4 for use in a method for reducing neuroinflammation in a mammal, wherein said method comprises contacting GPR120 in the mammal with an amount of said compound or said composition.

20 9. The compound of any one of claims 1-3 or the composition of claim 4 for use in a method for treating diabetes, pre-diabetes or metabolic syndrome, or one or more symptoms of each thereof in a mammal, wherein said method comprises contacting GPR120 in the mammal with a therapeutically effective amount of said compound or said composition.

25 10. The compound of any one of claims 1-3 or the composition of claim 4 for use in a method for treating steatohepatitis in a mammal, wherein said method comprises contacting GPR120 in the mammal with a therapeutically effective amount of said compound or said composition.

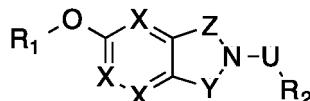
30 11. The compound of any one of claims 1-3 or the composition of claim 4 for use in a method for treating non-alcoholic steatohepatitis in a mammal, wherein said method comprises contacting GPR120 in the mammal with a therapeutically effective amount of said compound or said composition.

35 12. The compound of any one of claims 1-3 or the composition of claim 4 for use in a method for treating a disorder associated with, leading to, or resulting from neuroinflammation in a mammal, wherein said method comprises contacting GPR120 in the mammal with a therapeutically effective amount of said compound or said composition.

40 13. The compound of any one of claims 1-3 or the composition of claim 4 for use in a method for treating Alzheimer's disease, Parkinson's disease, frontotemporal dementia, amyotrophic lateral sclerosis or multi-system atrophy, or one or more symptoms of each thereof, wherein said method comprises contacting GPR120 in the patient with a therapeutically effective amount of said compound or said composition.

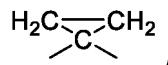
Patentansprüche

40 1. Verbindung der Formel:



wobei

50 jedes X unabhängig CH, CR₃ oder N ist;
 Y SO₂ ist;
 Z -CH₂-, -CH(CH₃)-, -C(CH₃)₂-,



-(CO)CH₂- oder -CHCH₂-

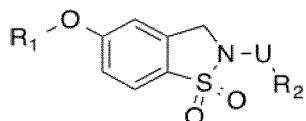
U CH₂, -CH (CH₃)-, -C(CH₃)₂- oder -CH₂CH₂- ist;

5 R₁ eine optional substituierte Alkylgruppe, eine optional substituierte 3-7-gliedrige Cycloalkyl- oder Heterocyclylgruppe, eine optional substituierte 6-gliedrige Arylgruppe, eine optional substituierte 5- oder 6-gliedrige Heteroarylgruppe, eine optional substituierte 5,6- oder eine 6,6-gliedrige bicyclische Heteroarylgruppe oder eine optional substituierte bicyclische Arylgruppe ist;

10 R₂ eine optional substituierte 3-7-gliedrige Cycloalkyl- oder Heterocyclylgruppe, eine optional substituierte 6-gliedrige Arylgruppe, eine optional substituierte 5- oder 6-gliedrige Heteroarylgruppe, eine optional substituierte 5,6- oder eine 6,6-gliedrige bicyclische Heteroarylgruppe oder eine optional substituierte bicyclische Arylgruppe ist; und

15 R₃ ein Halogen oder eine optional substituierte Alkyl- oder Alkoxygruppe ist.

2. Verbindung nach Anspruch 1 der Formel:



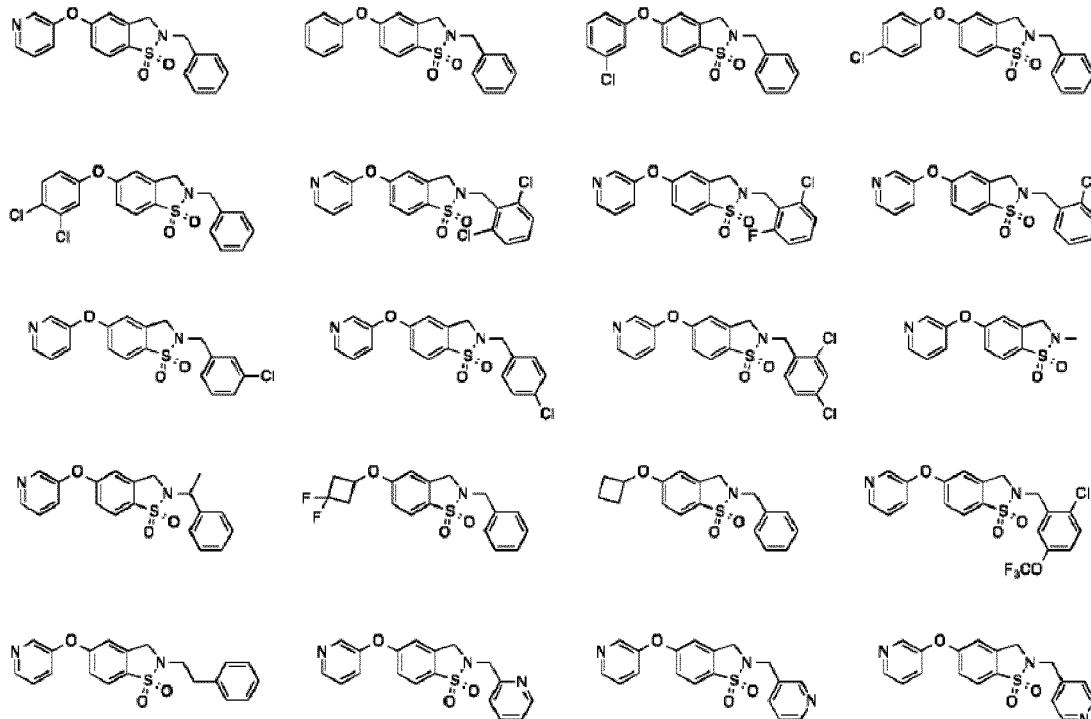
20 wobei

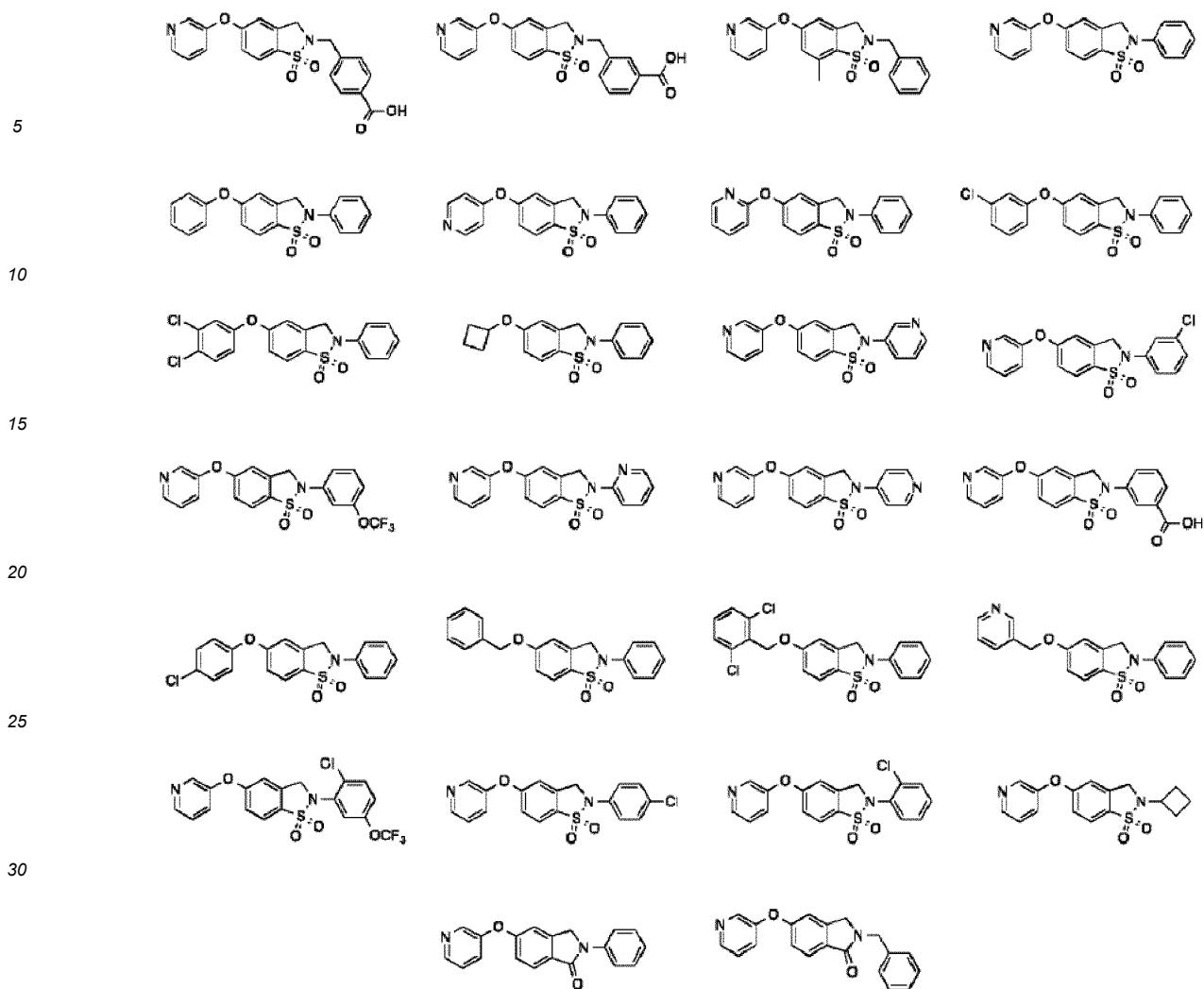
U CH₂, -CH (CH₃)-, -C(CH₃)₂- oder -CH₂CH₂- ist;

25 R₁ eine optional substituierte Alkylgruppe, eine optional substituierte 3-7-gliedrige Cycloalkyl- oder Heterocyclylgruppe, eine optional substituierte 6-gliedrige Arylgruppe, eine optional substituierte 5- oder 6-gliedrige Heteroarylgruppe, eine optional substituierte 5,6- oder eine 6,6-gliedrige bicyclische Heteroarylgruppe oder eine optional substituierte bicyclische Arylgruppe ist;

30 R₂ eine optional substituierte 3-7-gliedrige Cycloalkyl- oder Heterocyclylgruppe, eine optional substituierte 6-gliedrige Arylgruppe, eine optional substituierte 5- oder 6-gliedrige Heteroarylgruppe, eine optional substituierte 5,6- oder eine 6,6-gliedrige bicyclische Heteroarylgruppe oder eine optional substituierte bicyclische Arylgruppe ist.

3. Verbindung der Struktur





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4. Pharmazeutische Zusammensetzung, die eine Verbindung nach einem der Ansprüche 1-3 und einen pharmazeutisch verträglichen Exzipienten umfasst.

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5. Verbindung nach einem der Ansprüche 1-3 oder Zusammensetzung nach Anspruch 4 zur Verwendung in einem Verfahren zum Agonisieren von GPR120, wobei das Verfahren ein Inkontaktbringen des GPR120 mit der Verbindung oder der Zusammensetzung umfasst.

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6. Verbindung nach einem der Ansprüche 1 bis 3 oder Zusammensetzung nach Anspruch 4 zur Verwendung in einem Verfahren zum Modulieren des Stoffwechsels in einem Säuger, wobei das Verfahren ein Inkontaktbringen von GPR120 bei dem Säuger mit einer Menge der Verbindung oder der Zusammensetzung umfasst.

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7. Verbindung nach einem der Ansprüche 1-3 oder die Zusammensetzung nach Anspruch 4 zur Verwendung in einem Verfahren zum Reduzieren von Inflammation bei einem Säuger, wobei das Verfahren ein Inkontaktbringen von GPR120 bei dem Säuger mit einer Menge der Verbindung oder der Zusammensetzung umfasst.

8. Verbindung nach einem der Ansprüche 1-3 oder Zusammensetzung nach Anspruch 4 zur Verwendung in einem Verfahren zum Reduzieren von Neuroinflammation bei einem Säuger, wobei das Verfahren ein Inkontaktbringen von GPR120 bei dem Säuger mit einer Menge der Verbindung oder der Zusammensetzung umfasst.

9. Verbindung nach einem der Ansprüche 1-3 oder Zusammensetzung nach Anspruch 4 zur Verwendung in einem

Verfahren zum Behandeln von Diabetes, Prädiabetes oder metabolischem Syndrom oder einem oder mehreren Symptomen von jedem davon bei einem Säuger, wobei das Verfahren ein Inkontaktbringen von GPR120 bei dem Säuger mit einer therapeutisch wirksamen Menge der Verbindung oder der Zusammensetzung umfasst.

5 10. Verbindung nach einem der Ansprüche 1-3 oder Zusammensetzung nach Anspruch 4 zur Verwendung in einem Verfahren zum Behandeln von Steatohepatitis bei einem Säuger, wobei das Verfahren ein Inkontaktbringen von GPR120 bei dem Säuger mit einer therapeutisch wirksamen Menge der Verbindung oder der Zusammensetzung umfasst.

10 11. Verbindung nach einem der Ansprüche 1-3 oder Zusammensetzung nach Anspruch 4 zur Verwendung in einem Verfahren zum Behandeln von nichtalkoholischer Steatohepatitis bei einem Säuger, wobei das Verfahren ein Inkontaktbringen von GPR120 bei dem Säuger mit einer therapeutisch wirksamen Menge der Verbindung oder der Zusammensetzung umfasst.

15 12. Verbindung nach einem der Ansprüche 1 bis 3 oder Zusammensetzung nach Anspruch 4 zur Verwendung in einem Verfahren zum Behandeln einer Störung, die mit einer Neuroinflammation bei einem Säuger verbunden ist, zu dieser führt oder daraus resultiert, wobei das Verfahren ein Inkontaktbringen von GPR120 bei dem Säuger mit einer therapeutisch wirksamen Menge der Verbindung oder der Zusammensetzung umfasst.

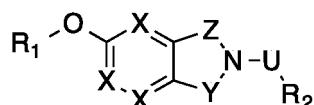
20 13. Verbindung nach einem der Ansprüche 1-3 oder Zusammensetzung nach Anspruch 4 zur Verwendung in einem Verfahren zum Behandeln von Alzheimer-Krankheit, Parkinson-Krankheit, frontotemporaler Demenz, amyotropher Lateralsklerose oder Multisystem-Atrophie oder einem oder mehreren Symptomen von jedem davon, wobei das Verfahren ein Inkontaktbringen von GPR120 bei dem Patienten mit einer therapeutisch wirksamen Menge der Verbindung oder der Zusammensetzung umfasst.

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Revendications

1. Composé de formule :

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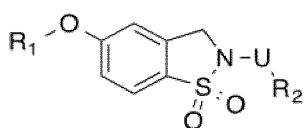
dans lequel

chaque X est indépendamment CH, CR₂, ou N :

Y est SO_3 :

40 Z est $-\text{CH}_2-$, $-\text{CH}(\text{CH}_3)-$, $-\text{C}(\text{CH}_3)_2-$.

2. Composé selon la revendication 1 de formule



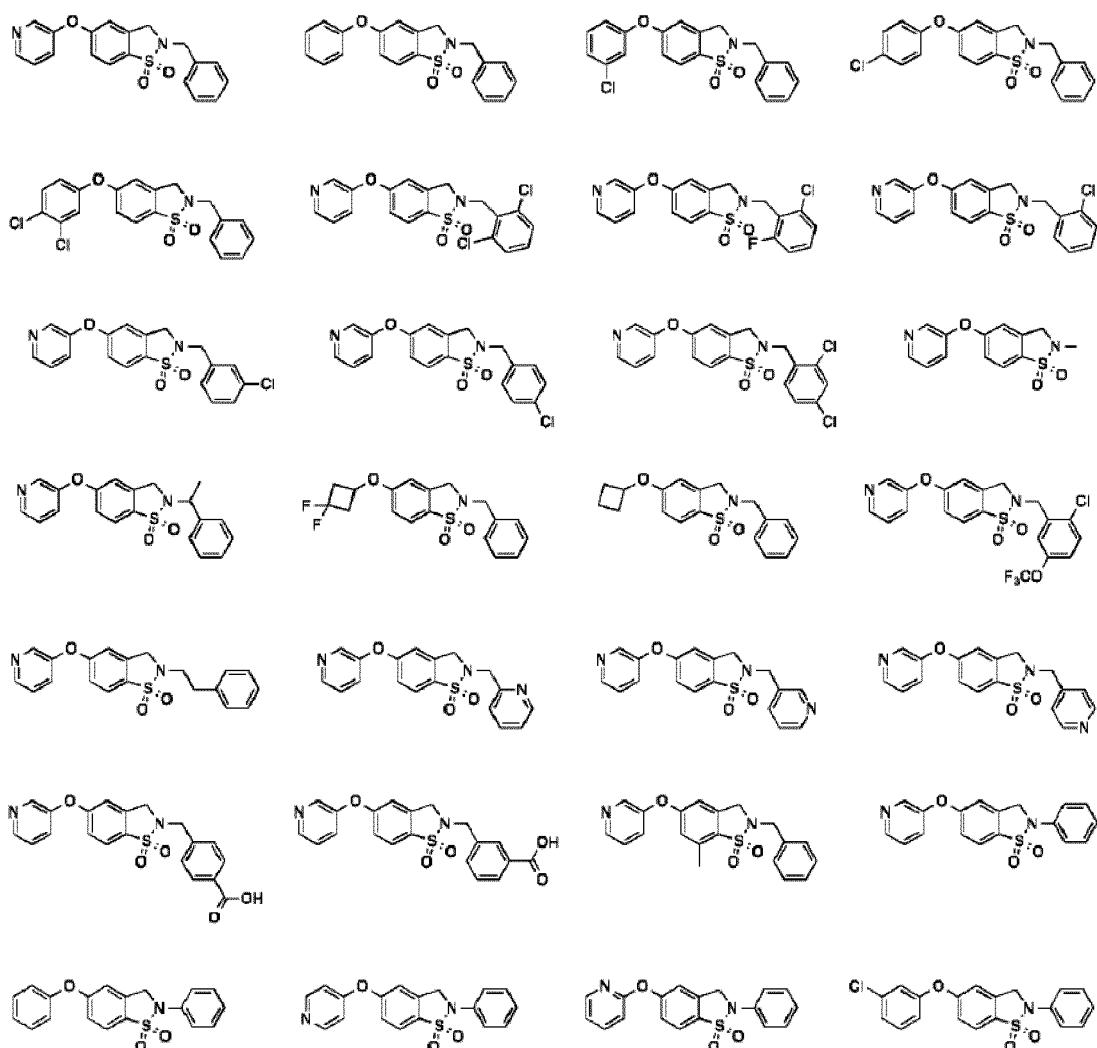
dans lequel

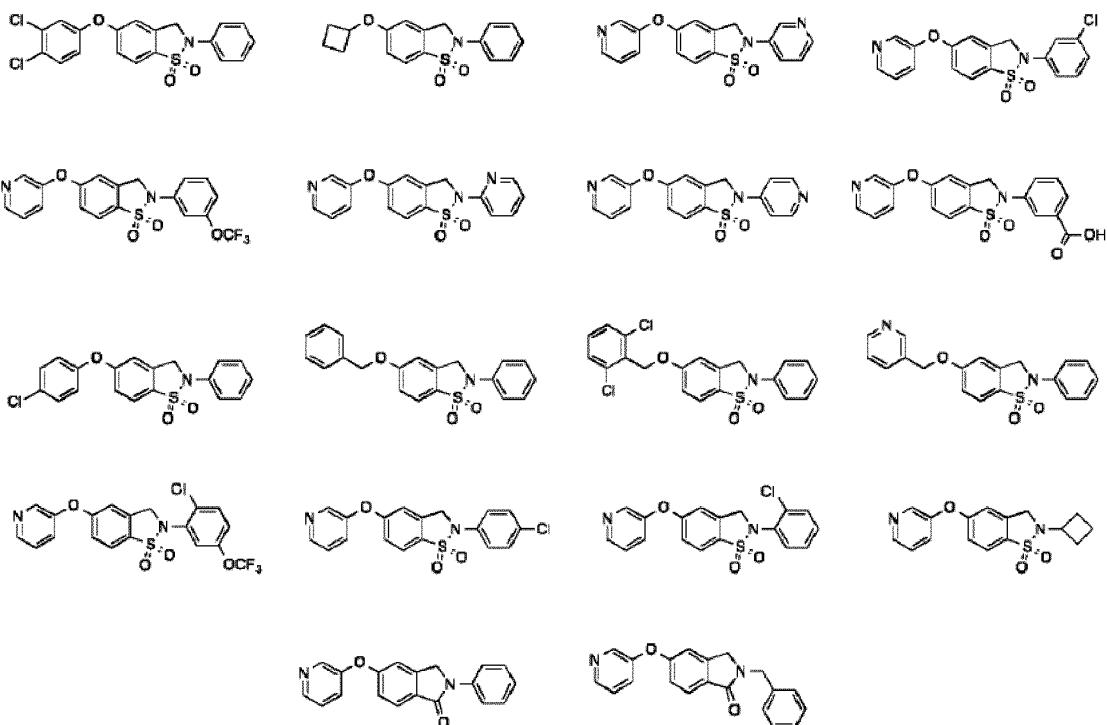
U est CH_2 , $-\text{CH}(\text{CH}_3)$, $-\text{C}(\text{CH}_3)_2$ ou $-\text{CH}_2\text{CH}_2$;

10 R_1 est un groupe alkyle facultativement substitué, un groupe cycloalkyle ou hétérocyclique à 3 à 7 chaînons facultativement substitué, un groupe aryle à 6 chaînons facultativement substitué, un groupe hétéroaryle à 5 ou 6 chaînons facultativement substitué, un groupe hétéroaryle bicyclique à 5,6 ou 6,6 chaînons facultativement substitué ou un groupe aryle bicyclique facultativement substitué ; et

15 R_2 est un groupe cycloalkyle ou hétérocyclique à 3 à 7 chaînons facultativement substitué, un groupe aryle à 6 chaînons facultativement substitué, un groupe hétéroaryle à 5 ou 6 chaînons facultativement substitué, un groupe hétéroaryle bicyclique à 5,6 ou 6,6 chaînons facultativement substitué ou un groupe aryle bicyclique facultativement substitué.

20 3. Composé de la structure





ou un tautomère de celui-ci, ou un isotopomère de celui-ci, ou un stéréoisomère de celui-ci, ou un sel pharmaceutiquement acceptable de chacun d'eux, ou un solvate pharmaceutiquement acceptable de chacun des précédents.

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11.

Composition pharmaceutique comprenant un composé selon l'une quelconque des revendications 1 à 3 et un excipient pharmaceutiquement acceptable.

Composé selon l'une quelconque des revendications 1 à 3 ou composition selon la revendication 4 pour une utilisation dans un procédé à effet agoniste de GPR120, dans lequel ledit procédé comprend la mise en contact de GPR120 avec ledit composé ou ladite composition.

Composé selon l'une quelconque des revendications 1 à 3 ou composition selon la revendication 4 pour une utilisation dans un procédé de modulation du métabolisme chez un mammifère, dans lequel ledit procédé comprend la mise en contact de GPR120 chez le mammifère avec une quantité dudit composé ou de ladite composition.

Composé selon l'une quelconque des revendications 1 à 3 ou composition selon la revendication 4 pour une utilisation dans un procédé de réduction d'inflammation chez un mammifère, dans lequel ledit procédé comprend la mise en contact de GPR120 chez le mammifère avec une quantité dudit composé ou de ladite composition.

Composé selon l'une quelconque des revendications 1 à 3 ou composition selon la revendication 4 pour une utilisation dans un procédé de réduction de neuroinflammation chez un mammifère, dans lequel ledit procédé comprend la mise en contact de GPR120 chez le mammifère avec une quantité dudit composé ou de ladite composition.

Composé selon l'une quelconque des revendications 1 à 3 ou composition selon la revendication 4 pour une utilisation dans un procédé de traitement du diabète, du prédiabète ou du syndrome métabolique, ou d'un ou de plusieurs symptômes de chacun de ceux-ci chez un mammifère, dans lequel ledit procédé comprend la mise en contact de GPR120 chez le mammifère avec une quantité thérapeutiquement efficace dudit composé ou de ladite composition.

Composé selon l'une quelconque des revendications 1 à 3 ou composition selon la revendication 4 pour une utilisation dans un procédé de traitement de la stéatohépatite chez un mammifère, dans lequel ledit procédé comprend la mise en contact de GPR120 chez le mammifère avec une quantité thérapeutiquement efficace dudit composé ou de ladite composition.

Composé selon l'une quelconque des revendications 1 à 3 ou composition selon la revendication 4 pour une utilisation

dans un procédé de traitement de la stéatohépatite non alcoolique chez un mammifère, dans lequel ledit procédé comprend la mise en contact de GPR120 chez le mammifère avec une quantité thérapeutiquement efficace dudit composé ou de ladite composition.

5 **12.** Composé selon l'une quelconque des revendications 1 à 3 ou composition selon la revendication 4 pour une utilisation dans un procédé de traitement d'un trouble associé à, entraînant ou résultant d'une neuroinflammation chez un mammifère, dans lequel ledit procédé comprend la mise en contact de GPR120 chez le mammifère avec une quantité thérapeutiquement efficace dudit composé ou de ladite composition.

10 **13.** Composé selon l'une quelconque des revendications 1 à 3 ou composition selon la revendication 4 pour une utilisation dans un procédé de traitement de la maladie d'Alzheimer, de la maladie de Parkinson, de la démence frontotemporale, de la sclérose latérale amyotrophique ou de l'atrophie multisystémique, ou d'un ou de plusieurs symptômes de chacun de ceux-ci, dans lequel ledit procédé comprend la mise en contact de GPR120 chez le patient avec une quantité thérapeutiquement efficace dudit composé ou de ladite composition.

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REFERENCES CITED IN THE DESCRIPTION

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Patent documents cited in the description

- US 62393619 [0001]
- US 4107288 A [0058]
- US 5145684 A [0058]
- US 20080167378 A [0207]
- WO 2008066131 A [0207]
- WO 2008103501 A [0207]
- WO 2008139987 A [0207]
- WO 2009147990 A [0207]
- US 20100130559 A [0207]
- WO 2010048207 A [0207]
- WO 2010080537 A [0207]
- WO 2011159297 A [0207]
- US 20110313003 A [0207]
- WO 2013139341 A [0207]
- WO 2014069963 A [0207]
- US 20140275172 A [0207]
- US 20140275179 A [0207]
- WO 20140275182 A [0207]
- WO 2014059232 A [0207]
- WO 2014159794 A [0207]
- US 20140275173 A [0207]
- WO 2010104195 A [0207]

Non-patent literature cited in the description

- Remington's Pharmaceutical Sciences. Mack Publishing Co, 1995 [0055]
- Remington's Pharmaceutical Sciences. Mack Publishing Company, 1990 [0060]
- Data for diabetes. World Health Organization [0207]
- **HIRASAWA et al.** *Nat. Med.*, 2005, vol. 11, 90-94 [0207]
- OH et al. *Cell*, 2010, vol. 142, 687-698 [0207]
- ICHIMURA et al. *Nature*, 2012, vol. 483, 350-354 [0207]
- CORNALL et al. *Drug Disc. Today*, 2014, vol. 19, 670-679 [0207]
- NOBILI et al. *PLOSone*, 2014, vol. 9, e88005 [0207]
- WELLHAUSER et al. *J Neuroinflamm*, 2014, vol. 11, 60 [0207]
- DRAGANO et al. *J Neuroinflamm*, 2017, vol. 17, 91 [0207]
- HENEKA et al. *Nature*, 2013, vol. 493, 674 [0207]
- YAN et al. *Immunity*, 2013, vol. 38, 1154 [0207]
- TAN et al. *Cell Death Dis*, 2014, vol. 5, e1382 [0207]
- KAUSHAL et al. *Cell Death Differentiation*, 2015, vol. 22, 1676 [0207]
- SUZUKI et al. *J. Med. Chem.*, 2008, vol. 51, 7640-7644 [0207]
- HARA et al. *Naunyn Schmied. Arch. Pharmacol.*, 2009, vol. 380, 247-255 [0207]
- SHIMPUKADE et al. *J. Med. Chem.*, 2012, vol. 55, 4511-4515 [0207]
- HUDSON et al. *Mol Pharmacol.*, 2013, vol. 84, 710-725 [0207]
- OH et al. *Nat. Med.*, 2014, vol. 20, 942-947 [0207]
- SPARKS et al. *Bioorg. Med. Chem. Lett.*, 2014, vol. 24, 3100-3103 [0207]
- TANAKA et al. *Naunyn-Schmiedeberg's Arch Pharmacol.*, 2008, vol. 377, 523-527 [0207]
- LU et al. *Am. J. Gastrointest. Liver Physiol.*, 2012, vol. 303, G367-G376 [0207]
- SUCKOW et al. *J. Bio. Chem.*, 2014, vol. 289, 15751-15763 [0207]